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Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections (Review)

Shaikh N, Spingarn RB, Hum SW

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Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD010657.

DOI: [10.1002/14651858.CD010657.pub2](https://doi.org/10.1002/14651858.CD010657.pub2).

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	5
METHODS	5
RESULTS	7
Figure 1.	8
Figure 2.	9
Figure 3.	10
Figure 4.	12
Figure 5.	13
Figure 6.	14
Figure 7.	15
Figure 8.	16
Figure 9.	17
Figure 10.	18
Figure 11.	19
Figure 12.	20
Figure 13.	21
DISCUSSION	21
AUTHORS' CONCLUSIONS	22
ACKNOWLEDGEMENTS	22
REFERENCES	23
CHARACTERISTICS OF STUDIES	36
DATA	94
Test 1. Ultrasound.	95
Test 2. Ultrasound for high-grade VUR.	95
Test 3. Ultrasound Renal Units.	95
Test 4. Ultrasound for high-grade VUR (Renal Units).	96
Test 5. DMSA.	96
Test 6. DMSA for high-grade VUR.	96
Test 7. DMSA Renal-Units.	97
Test 8. DMSA for high-grade VUR (Renal Units).	97
APPENDICES	97
CONTRIBUTIONS OF AUTHORS	100
DECLARATIONS OF INTEREST	100
SOURCES OF SUPPORT	100
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	100
INDEX TERMS	100

[Diagnostic Test Accuracy Review]

Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections

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ABSTRACT

Background

There is considerable interest in detecting vesicoureteral reflux (VUR) because its presence, especially when severe, has been linked to an increased risk of urinary tract infections and renal scarring. Voiding cystourethrography (VCUG), also known as micturating cystourethrography, is the gold standard for the diagnosis of VUR, and the grading of its severity. Because VCUG requires bladder catheterisation and exposes children to radiation, there has been a growing interest in other screening strategies that could identify at-risk children without the risks and discomfort associated with VCUG.

Objectives

The objective of this review is to evaluate the accuracy of two alternative imaging tests - the dimercaptosuccinic acid renal scan (DMSA) and renal-bladder ultrasound (RBUS) - in diagnosing VUR and high-grade VUR (Grade III-V VUR).

Search methods

We searched MEDLINE, EMBASE, BIOSIS, and the Cochrane Register of Diagnostic Test Accuracy Studies from 1985 to 31 March 2016. The reference lists of relevant review articles were searched to identify additional studies not found through the electronic search.

Selection criteria

We considered published cross-sectional or cohort studies that compared the results of the index tests (DMSA scan or RBUS) with the results of radiographic VCUG in children less than 19 years of age with a culture-confirmed urinary tract infection.

Data collection and analysis

Two authors independently applied the selection criteria to all citations and independently abstracted data. We used the bivariate model to calculate summary sensitivity and specificity values.

Main results

A total of 42 studies met our inclusion criteria. Twenty studies reported data on the test performance of RBUS in detecting VUR; the summary sensitivity and specificity estimates were 0.44 (95% CI 0.34 to 0.54) and 0.78 (95% CI 0.68 to 0.86), respectively. A total of 11 studies reported data on the test performance of RBUS in detecting high-grade VUR; the summary sensitivity and specificity estimates were 0.59 (95% CI 0.45 to 0.72) and 0.79 (95% CI 0.65 to 0.87), respectively. A total of 19 studies reported data on the test performance of DMSA in detecting VUR; the summary sensitivity and specificity estimates were 0.75 (95% CI 0.67 to 0.81) and 0.48 (95% CI 0.38 to 0.57), respectively. A total

of 10 studies reported data on the accuracy of DMSA in detecting high-grade VUR. The summary sensitivity and specificity estimates were 0.93 (95% CI 0.77 to 0.98) and 0.44 (95% CI 0.33 to 0.56), respectively.

Authors' conclusions

Neither the renal ultrasound nor the DMSA scan is accurate enough to detect VUR (of all grades). Although a child with a negative DMSA test has an < 1% probability of having high-grade VUR, performing a screening DMSA will result in a large number of children falsely labelled as being at risk for high-grade VUR. Accordingly, the usefulness of the DMSA as a screening test for high-grade VUR should be questioned.

PLAIN LANGUAGE SUMMARY

The accuracy of two imaging tests in detecting vesicoureteral reflux

Some children are born with an anatomic abnormality that allows backwards flow of urine from the bladder to the kidney. This is called vesicoureteral reflux or VUR. Children with VUR have more urinary tract infections and develop more renal scars than children without VUR. This is especially the case if VUR is severe. As such, clinicians are interested in finding out which children have VUR. Unfortunately, testing for VUR (using a voiding cystourethrogram or a VCUG or MCUG) involves bladder catheterisation and exposure to radiation. Accordingly, clinicians are interested in finding alternative tests that could replace the VCUG. The authors compared the accuracy of two other imaging tests (ultrasound and DMSA renal scan) to see whether these could replace the VCUG test. Neither test was found to be sufficiently accurate to replace the VCUG test. Although the DMSA scan seems to be good at ruling out high-grade VUR, it falsely labels many children as being at risk for high-grade VUR. Accordingly, DMSA does not appear to be useful as a screening test.

SUMMARY OF FINDINGS

Summary of findings 1. Renal-bladder ultrasound (RBUS) and ⁹⁹Tc-Dimercaptosuccinic acid (DMSA) in the detection of vesicoureteral reflux (VUR)

Accuracy of RBUS and DMSA in detecting VUR in a population of 1000 children*

Population: 1000 children with urinary tract infection (UTI) of which 400 have VUR

Setting: not specified

Tests: DMSA conducted within 1 month of the diagnosis of UTI, RBUS

Reference test: radiographic voiding cystourethrogram

Test and cut-off	No. of studies (participants)	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)	No. with a false negative test (missed cases)	No. with a false positive test (over-diagnosed)	Post-test probability of VUR given a positive test	Post-test probability of VUR given a negative test	Heterogeneity between studies	High risk of bias studies
Ultra-sound	20 (3726)	0.44 (0.34 to 0.54)	0.78 (0.68 to 0.86)	224	132	57%	32%	High	13 of 20
DMSA	19 (3863)	0.75 (0.67 to 0.81)	0.48 (0.38 to 0.57)	100	312	49%	26%	Moderate	10 of 19

*Assuming a pretest probability of 40% (see text for justification)

Summary of findings 2. Renal-bladder ultrasound (RBUS) and ⁹⁹Tc-Dimercaptosuccinic acid (DMSA) in the detection of high-grade vesicoureteral reflux (VUR) (VUR III-V)

Accuracy of RBUS and DMSA in detecting high-grade VUR in a population of 1000 children

Population: 1000 children with urinary tract infection (UTI) of which 130 have VUR III-V

Setting: not specified

Tests: DMSA conducted within 1 month of the diagnosis of UTI, RBUS

Reference test: radiographic voiding cystourethrogram

Test and cut-off	No. of studies	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)	No. with a false negative test	No. with a false positive test	Post-test probability of high-grade VUR given a positive test	Post-test probability of high-grade VUR given a negative test	Heterogeneity	High risk of bias studies
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	(partici- pants)			(missed cases)	(over-diag- nosed)			between studies	
Ultra- sound	11 (2498)	0.59 (0.45 to 0.72)	0.79 (0.65 to 0.88)	53	183	30%	8%	Moderate	6 of 11
DMSA	10 (2499)	0.93 (0.77 to 0.98)	0.44 (0.33 to 0.56)	9	487	20%	< 1%	Moderate	5 of 10
* Assuming a pretest probability of 13% (see text for justification)									

BACKGROUND

Although the prevention of permanent renal scarring represents the ultimate goal of management strategies for childhood urinary tract infection (UTI), controversy exists about how this should be achieved. Until recently, the prevailing management approach in the United States has focused on the identification and treatment of the subset of children with vesicoureteral reflux (VUR), a congenital anatomic abnormality that enables retrograde flow of urine from the bladder to the kidney and therefore is thought to facilitate the ascent of infection to the kidney.

Voiding cystourethrography (VCUG), also known as micturating cystourethrography, is the gold standard for the diagnosis of VUR and the grading of its severity. During the VCUG the child is catheterized, and radiocontrast material is used to fill the bladder. The child is then asked to void (younger children often void automatically). Fluoroscopy is used to visualize the anatomy of the bladder and the urethra. Movement of the contrast medium into the ureters indicates VUR. VUR is graded on scale of I to V, with V being the most severe. Grade III-V VUR is considered high-grade and may be present in up to 13% of children with febrile UTIs (Shaikh 2014).

Until recently, children with UTI underwent routine VCUG examinations and those with VUR were treated with prophylactic antibiotics and/or surgery. Increasingly, however, it has been recognized that the aggressive detection and treatment of VUR may not lead to improvements in long-term outcomes (Nagler 2011). Nevertheless, there is still considerable interest in detecting VUR, especially VUR that is severe. The Swedish reflux study showed that antibiotic treatment of girls with high-grade VUR was associated with significantly fewer infections and reduced renal scarring compared with placebo (Brandstrom 2010). A recent meta-analysis found that the prevalence of renal scarring was 2.6 times (95% CI 1.7 to 3.9) higher among children with VUR than among children with no VUR (41% versus 17%; $P = 0.001$) (Shaikh 2010). The RIVUR study found that prophylactic antibiotics halved the rate of reinfection in children with VUR (Hoberman 2014). The American Academy of Pediatrics (AAP) guidelines recommend that children aged from 2 to 24 months with recurrent UTIs should be screened for VUR with a VCUG (AAP 2011). The United Kingdom's National Institute for Health and Care Excellence (NICE) guidelines recommend obtaining a VCUG in infants younger than six months of age with recurrent UTI (NICE 2007).

Index test(s)

One approach that has been advocated as an alternative to VCUGs is the performance of ^{99}Tc -Dimercaptosuccinic acid (DMSA) renal scans within two weeks of the UTI. In this test, radiolabelled DMSA is injected through an IV catheter and DMSA uptake by the kidneys is visualized with a gamma camera approximately two hours later, enabling the radiologist to see the uptake of DMSA by different parts of the kidney. If tubular cell function is impaired because of pyelonephritis, the scan will show photon-deficient areas. A second approach is to use the renal-bladder ultrasound (RBUS) as a screening test for VUR. RBUS is useful for detecting a variety of anatomic abnormalities, but its accuracy in diagnosing VUR or high-grade VUR has not been systematically studied.

Clinical pathway

Although guidelines vary, most young children with UTI will have a routine RBUS performed soon after the first UTI. VCUG is usually reserved for children with an abnormal RBUS or children with multiple UTIs. If VUR is detected, controversy exists regarding which children, if any, should be treated with prophylactic antibiotics and/or surgery. VUR resolves spontaneously and without sequelae in the large majority of children. DMSAs are not routinely performed in children with UTIs.

Alternative test(s)

Several other tests, such as inflammatory markers (e.g. procalcitonin) have been recently proposed as alternatives to VCUG. However, because they have been reviewed elsewhere, they were not considered here.

Rationale

Because VCUG requires bladder catheterization, there has been growing interest in other screening strategies that could identify at-risk children without the risks and discomfort associated with VCUG. Both DMSA and RBUS have been put forth as possible tests that could replace the VCUG in the detection of VUR. A systematic literature review on this topic will help clinicians to decide if a DMSA or a RBUS is an appropriate initial screening test for concerns regarding the presence of VUR.

OBJECTIVES

The primary objective of this review is to evaluate the diagnostic accuracy of DMSA and RBUS in identifying VUR and high-grade VUR.

Secondary objectives

A secondary objective is to compare the rate of adverse events between DMSA scans and RBUS.

METHODS

Criteria for considering studies for this review

Types of studies

Cross-sectional and cohort designs were acceptable for inclusion. We excluded case-control studies because they are known to inflate estimates of sensitivity and specificity.

Participants

We considered published studies that compared the results of an index test (DMSA scan or RBUS) with the results of a radiographic VCUG in children from zero to 19 years of age with a culture-confirmed episode of UTI. Studies were considered whether or not they included children with previous UTIs. UTI was defined as growth of $\geq 10^4$ colony-forming units (CFU)/mL organisms from a catheterized specimen, $\geq 10^5$ CFU/mL organisms from a clean catch, midstream, or bag specimen, or any growth from a suprapubic specimen (Hoberman 1994). Studies that did not meet these minimum criteria were excluded.

Index tests

Studies in which DMSA scan was performed were included only if the DMSA was conducted within the first month of the UTI diagnosis. Planar DMSA scans are two-dimensional images of

the distribution of radioisotope uptake, whereas SPECT (single-photon emission computed tomography) DMSA scans reconstruct the three-dimensional distribution by taking multiple images from different angles. For the purpose of this analysis, any photopenia on a DMSA scan, with or without loss of contours, was considered positive. Studies in which RBUS was performed for the evaluation of UTI were included regardless of whether or not the timing of the RBUS was specified in the manuscript. Almost all centres we are aware of conduct the RBUS within the first two months after the diagnosis of a UTI. An ultrasound with any abnormality was considered positive.

Target conditions

VUR (any grade) and high-grade VUR (VUR grades III to V) were the target conditions.

Reference standards

VCUG is the reference standard for diagnosing VUR. VUR is graded from I to V according to the International Reflux Study criteria (IRSC 1981); Grades III to V are considered high-grade.

Search methods for identification of studies

Electronic searches

We searched MEDLINE (OvidSP) to 31 March 2016 and EMBASE (OvidSP), BIOSIS, and the Cochrane Register of Diagnostic Test Accuracy Studies up to 6 February 2014. DMSA scans were not used in children until the late 1980s and ultrasound technology has improved greatly since the late 1980's, so searches were limited to the years 1985 to the present.

See [Appendix 1](#) for search strategies.

Searching other resources

1. Reference lists of important review articles retrieved from searches.
2. Reference lists of relevant diagnostic test accuracy studies.

Data collection and analysis

Two authors independently applied the selection criteria to all citations (titles and abstracts).

Selection of studies

Two authors independently assessed titles, abstracts and, if necessary, the full text of studies found using the search strategy to determine which studies satisfied the inclusion criteria. Disagreements were resolved by discussion.

Data extraction and management

Data extraction was carried out independently by two authors using standardized data extraction forms. When possible, study authors were contacted for clarification. Studies not published in English were translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was used in the analyses.

For each study meeting our inclusion criteria, we abstracted the following information.

- Setting of enrolment (outpatient, emergency department, inpatient)
- Referral source (self-referred, referred by a specialist)
- Age range of participants
- Excluded children with genitourinary abnormalities? (yes, no)
- Excluded children with previous UTI? (yes, no)
- All children in study febrile (whether measured or tactile)? (yes, no)
- Used paediatric urine collection bags to collect urine specimen? (yes, no)
- Maximal delay in DMSA scan (within one week, one to two weeks, two to four weeks)
- Type of DMSA (planar versus. SPECT)
- Rate and type of adverse events from DMSA scan or RBUS.

Two by two tables were constructed independently by each author from the data in the publication. Only studies for which two by two data were available (or could be reconstructed) were included. Disagreements between authors were resolved by discussion.

Assessment of methodological quality

Two authors independently assessed the methodological quality of each included study using a four-domain tool (patient selection, the index test, the reference standard, and flow/timing) adapted from QUADAS-2 (Whiting 2011). QUADAS-2 is a validated tool specifically designed for review authors to evaluate quality of diagnostic accuracy studies. We adapted QUADAS-2 specifically for our review (see [Appendix 2](#)).

Statistical analysis and data synthesis

The primary analysis compared the accuracy of each index test (DMSA or RBUS) with the VCUG in the diagnosis of VUR of any grade. Because high-grade VUR (Grades III to V) is associated with a higher risk of scarring (Shaikh 2010), a secondary analysis was performed using high-grade VUR as the outcome.

For the analysis, we chose the bivariate model because we felt that studies mostly used uniform thresholds (any abnormality for RBUS and any photopenia for DMSA). In the bivariate model, the logit-transformed sensitivity and specificity for each study are modelled jointly, and the correlation between them, across studies, is also taken into account. This method provides a summary estimate of sensitivity and specificity for each index test, along with a 95% confidence interval (95% CI). Results are then transformed back to the original scale and plotted in the ROC space.

We compared the index tests indirectly and directly. In the indirect comparison, we used the bivariate model to calculate summary sensitivity and specificity values separately for each test using data from all studies using test type as a covariate. Some studies directly compared (Hayen 2010) the accuracy of the two index tests (both index tests were performed in the same study); analysis of such studies may be less subject to bias.

SAS® software was used to perform all analyses.

Investigations of heterogeneity

We conducted a meta-regression to investigate heterogeneity in diagnostic accuracy across studies. We chose five variables a priori that we felt could explain some of the of heterogeneity. Each

variable was included in the analysis as a study-level covariate and its effect on sensitivity and specificity was examined. This investigation was only performed if there were at least 10 studies (and least four studies for each category of the covariate).

The five covariates chosen are listed below. Two of the covariates are only applicable for studies of DMSA scan accuracy.

- All studies: whether or not fever was required for inclusion
- All studies: whether or not children with UTI diagnosed from a perineal bag collected specimen were included (because specimens obtained using a perineal bag have a high false positive rate)
- All studies: number of UTIs prior to enrolment (0 versus ≥ 1) (because children with recurrent UTIs are more likely to have VUR)
- Studies of DMSA scan accuracy: timing of DMSA scan (< 14 days versus < 30 days) after diagnosis of UTI (because DMSA scan sensitivity decreases substantively after two weeks ([Stokland 1996](#)))

- Studies of DMSA scan accuracy: whether a planar or a SPECT technique for the DMSA scan was used (because SPECT DMSA scans have lower specificity than planar DMSA scans ([Craig 2000](#))).

Sensitivity analyses

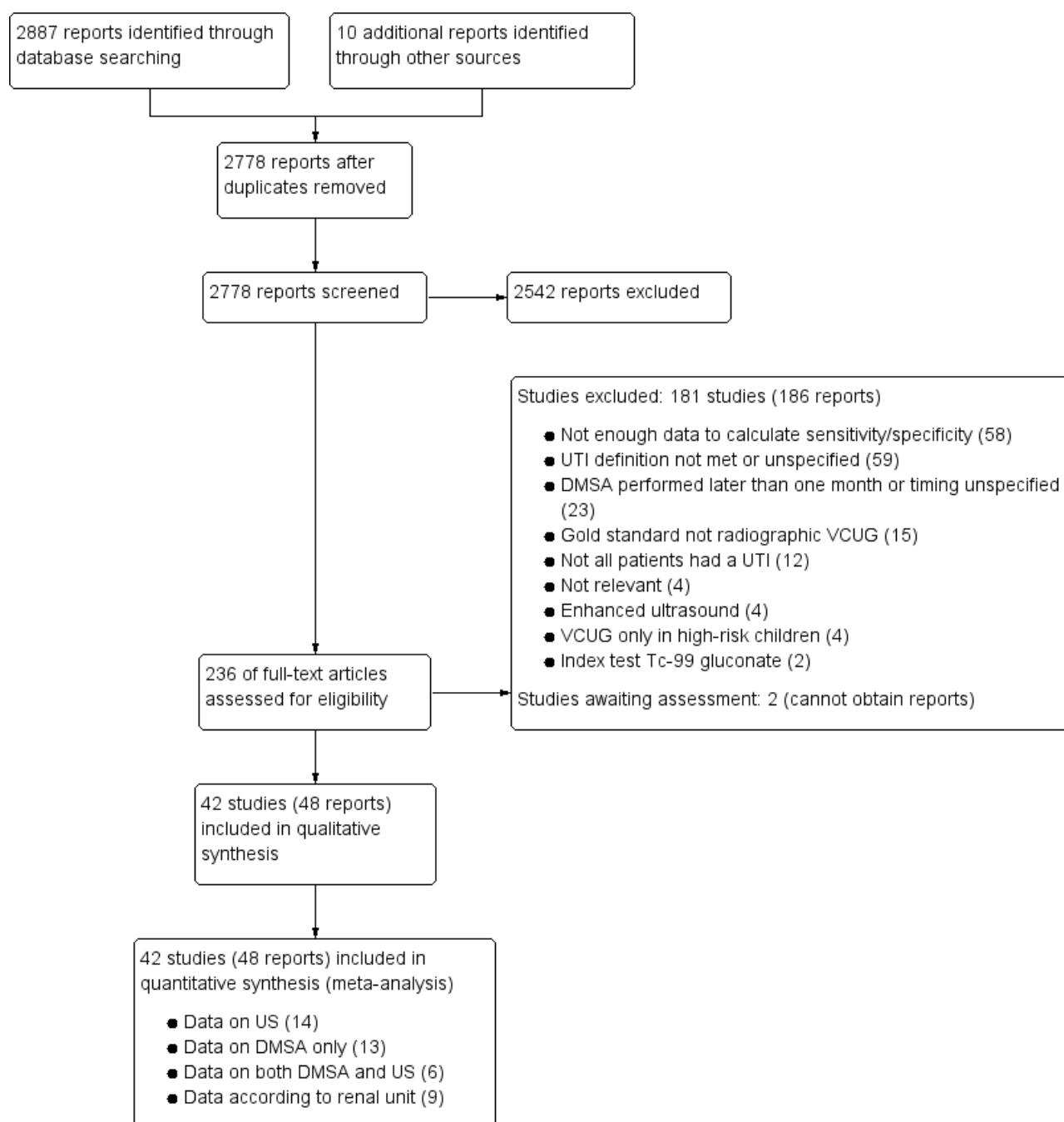
To investigate robustness of the results we limited the analysis to 1) only studies at low risk of bias (QUADAS-2, item), and 2) only studies with no applicability concerns.

RESULTS

Results of the search

The results of the search strategy are shown in [Figure 1](#). Of the 2778 articles found through the search strategy, 238 full text articles were retrieved and reviewed. A total of 42 studies met all the inclusion criteria, and all were included in the meta-analysis. 30/42 (71%) studies enrolled only children with a first UTI, and 27/42 (64%) studies enrolled only children with a fever. In studies in which DMSA scan was performed, 25/28 (89%) conducted the scan within 14 days of UTI diagnosis, and all but one used planar DMSA imaging.

Figure 1. Study flow diagram.



Data on the accuracy of ultrasound and DMSA in detecting VUR were available from 20 and 19 studies, respectively; six studies provided data on both tests. Data on the accuracy of ultrasound and DMSA in detecting high-grade VUR were available from 11 and 10 studies, respectively. Only one study included data on the accuracy of ultrasound at the level of the renal unit. Nine studies included data on the accuracy of DMSA in detecting VUR at the level of the renal unit; four of these provided data on high-grade VUR. A listing of the excluded studies and their characteristics is provided in [Characteristics of excluded studies](#).

Prior to publication a final search (31 March 2016) was conducted. The references identified will be assessed in a future update of this review.

Methodological quality of included studies

The largest methodological limitations of the included studies are related to the selection of the patients ([Figure 2](#); [Figure 3](#)). Of the 42 studies included, we judged that patient selection led to increased risk of bias in 11 (26%) and to applicability concerns in 21 (50%). We had relatively little concerns with regards to the way the reference standard was performed. Flow and timing issues were noted in four studies. Overall, there were concerns with risk of bias

or applicability in 27 (64%) studies. Other limitations not reflected in the figures include the use of paediatric urine collection bags in 10 studies (23%).

Figure 2. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies

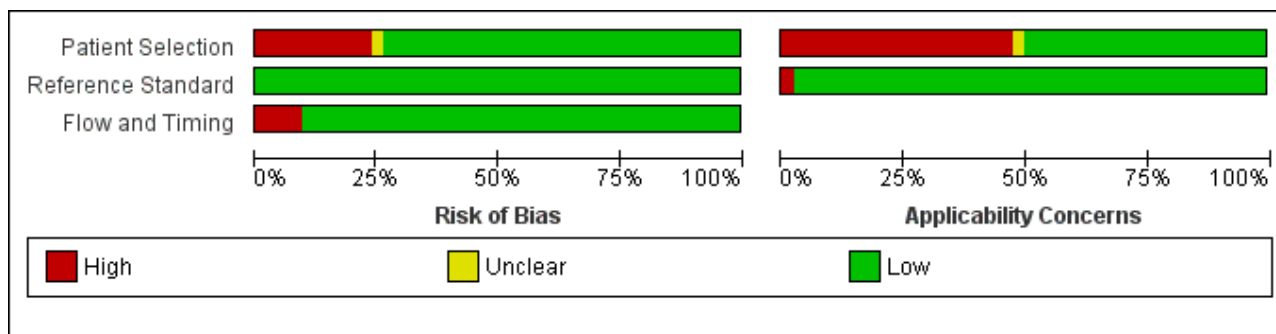
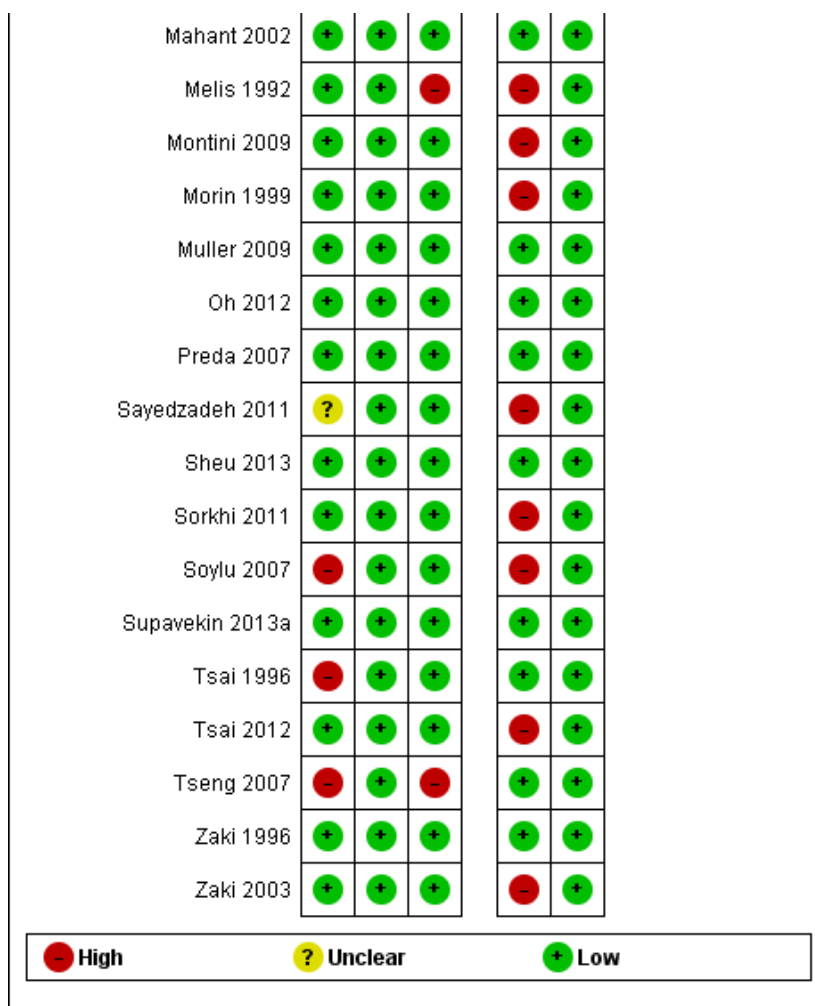


Figure 3. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study

	Risk of Bias			Applicability Concerns	
	Patient Selection	Reference Standard	Flow and Timing	Patient Selection	Reference Standard
Agras 2007	+	+	+	-	+
Alon 1986	+	+	+	+	+
Alon 1999	-	+	-	+	+
Ansari Gilani 2010	+	+	-	+	+
Ataei 2005	+	+	+	-	+
Ataei 2008	+	+	+	-	+
Calisti 2005	+	+	+	+	+
Camacho 2004	+	+	+	+	+
Cascio 2002	-	+	+	-	+
Cleper 2004	-	+	+	-	+
Doganis 2007	+	+	+	+	+
Donoso 2004	+	+	+	?	+
El Shenoufy 2009	+	+	+	-	+
Fernandez-Menendez 2003	+	+	+	+	+
Goldman 2000	+	+	+	-	+
Hoberman 2003	+	+	+	+	+
Ilyas 2002	-	+	+	+	+
Ismaili 2011	+	+	+	-	+
Jakobsson 1992	+	+	+	+	+
Kim 2006	-	+	+	-	+
Lavocat 1997	+	+	+	-	+
Lee 2009a	-	+	+	+	-
Lee 2012a	-	+	+	-	+
Lin 2007	+	+	+	+	+
Lopez Sastre 2007	+	+	+	-	+
Mahant 2002	+	+	+	+	+

Figure 3. (Continued)



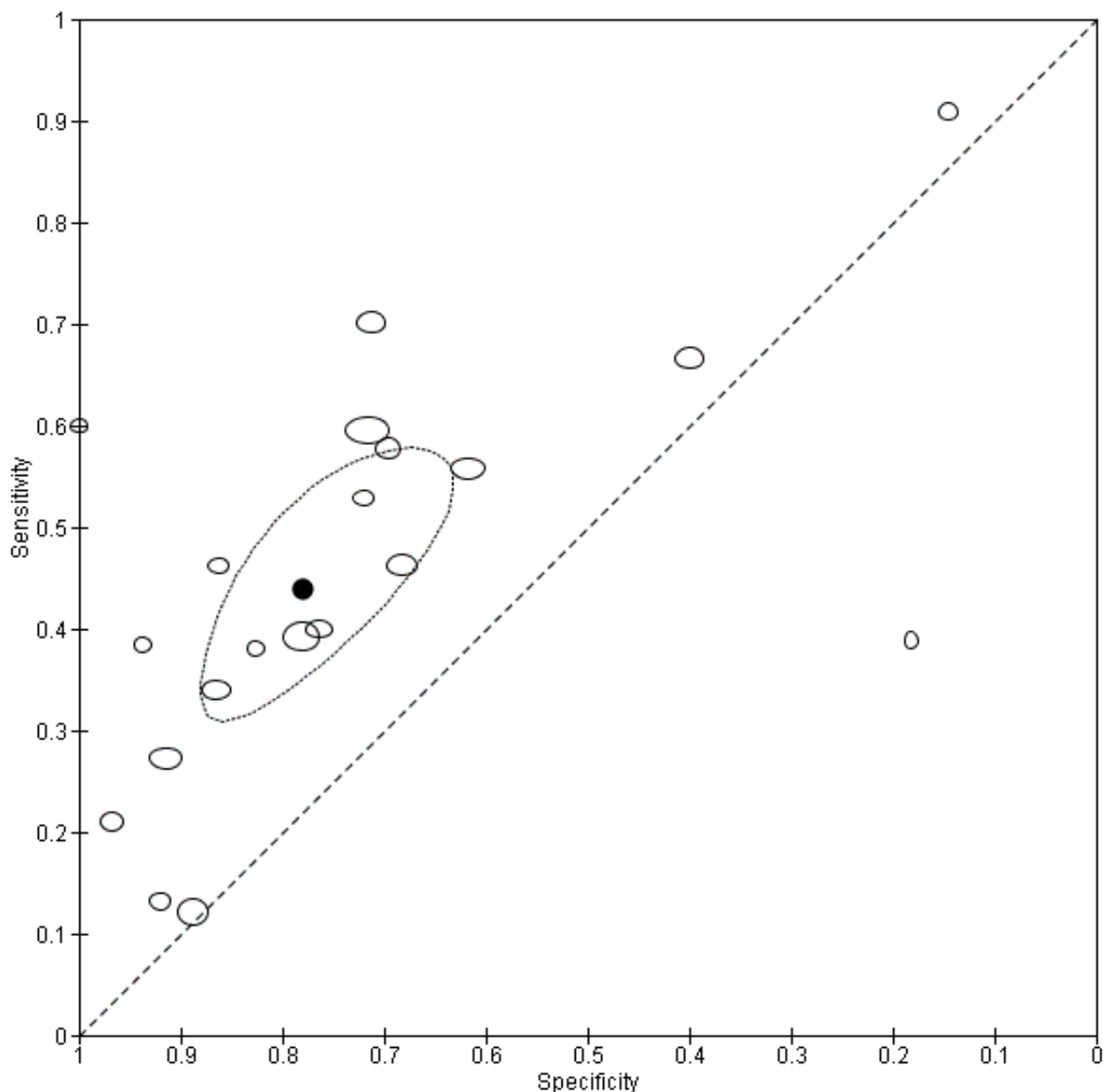
Findings

Ultrasound

Twenty studies reported data on the accuracy of ultrasound in detecting VUR. The summary sensitivity and specificity estimates were 0.44 (95% CI 0.34 to 0.54) and 0.78 (95% CI 0.68 to 0.86), respectively (Figure 4). Although there was substantial

heterogeneity between studies (Data table 1), none of the studies reported high sensitivity and specificity values. None of the covariates investigated in the meta-regression had a significant effect on either the sensitivity or specificity values. Limiting the analysis to low risk of bias studies resulted in an even lower summary specificity value (0.72, 95% CI 0.59 to 0.82).

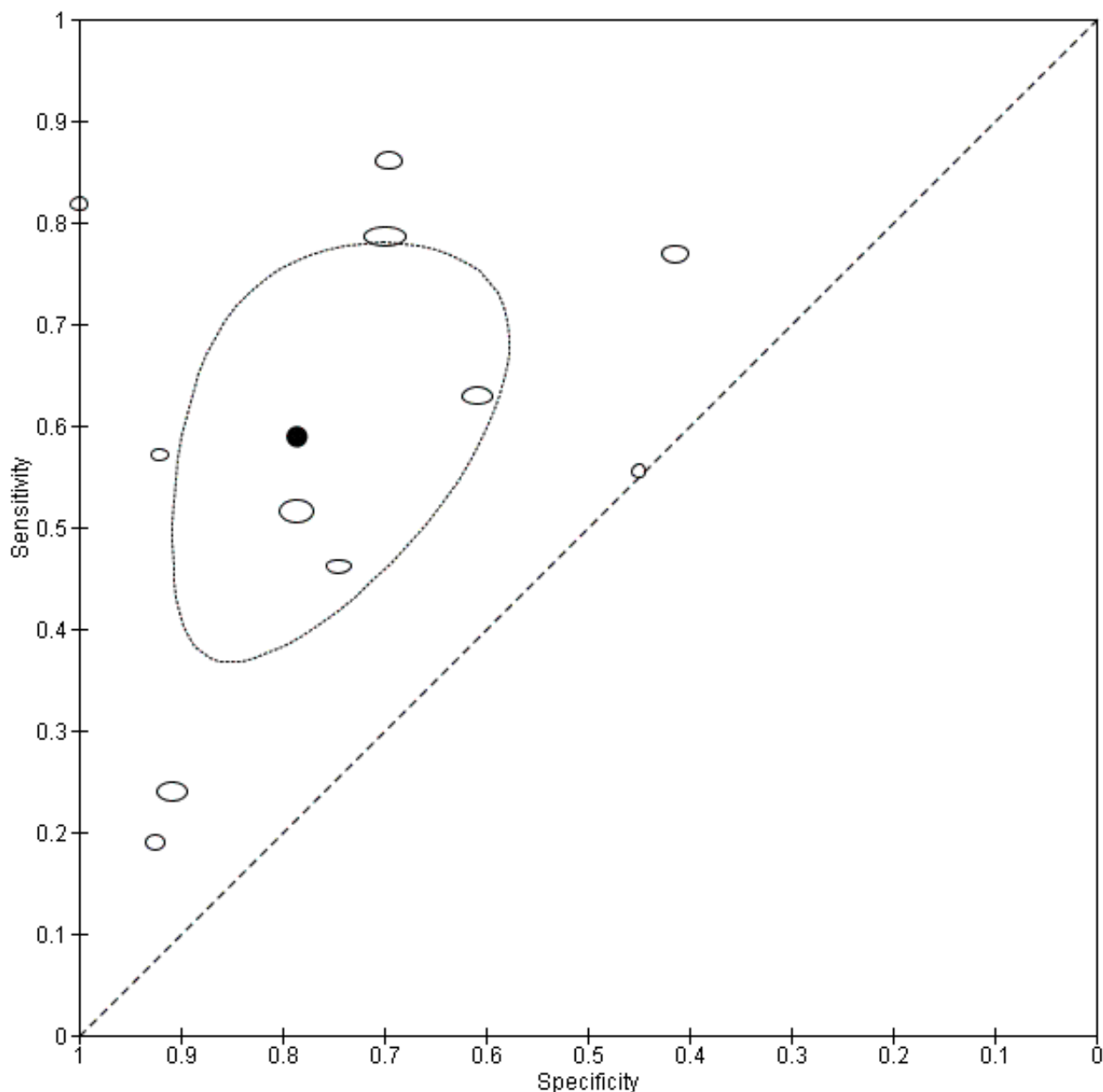
Figure 4. Ultrasound to detect VUR (all grades)



Eleven studies reported data on the accuracy of ultrasound in detecting high-grade VUR. The summary sensitivity and specificity estimates were 0.59 (95% CI 0.45 to 0.72) and 0.79 (95% CI 0.65 to 0.87), respectively (Figure 5). Although there was substantial heterogeneity between studies (Data table 2), only Kim 2006 reported sensitivity and specificity values close to 90%. The

use of paediatric urine collection bags explained some of the heterogeneity in the sensitivity estimates ($P = 0.045$); the sensitivity of ultrasound in studies where paediatric urine collection bags were and were not used was 0.78 (95% CI 0.55 to 0.91) and 0.49 (95% CI 0.33 to 0.66), respectively. Sensitivity analysis did not substantively alter the summary estimates.

Figure 5. Ultrasound to detect high-grade VUR



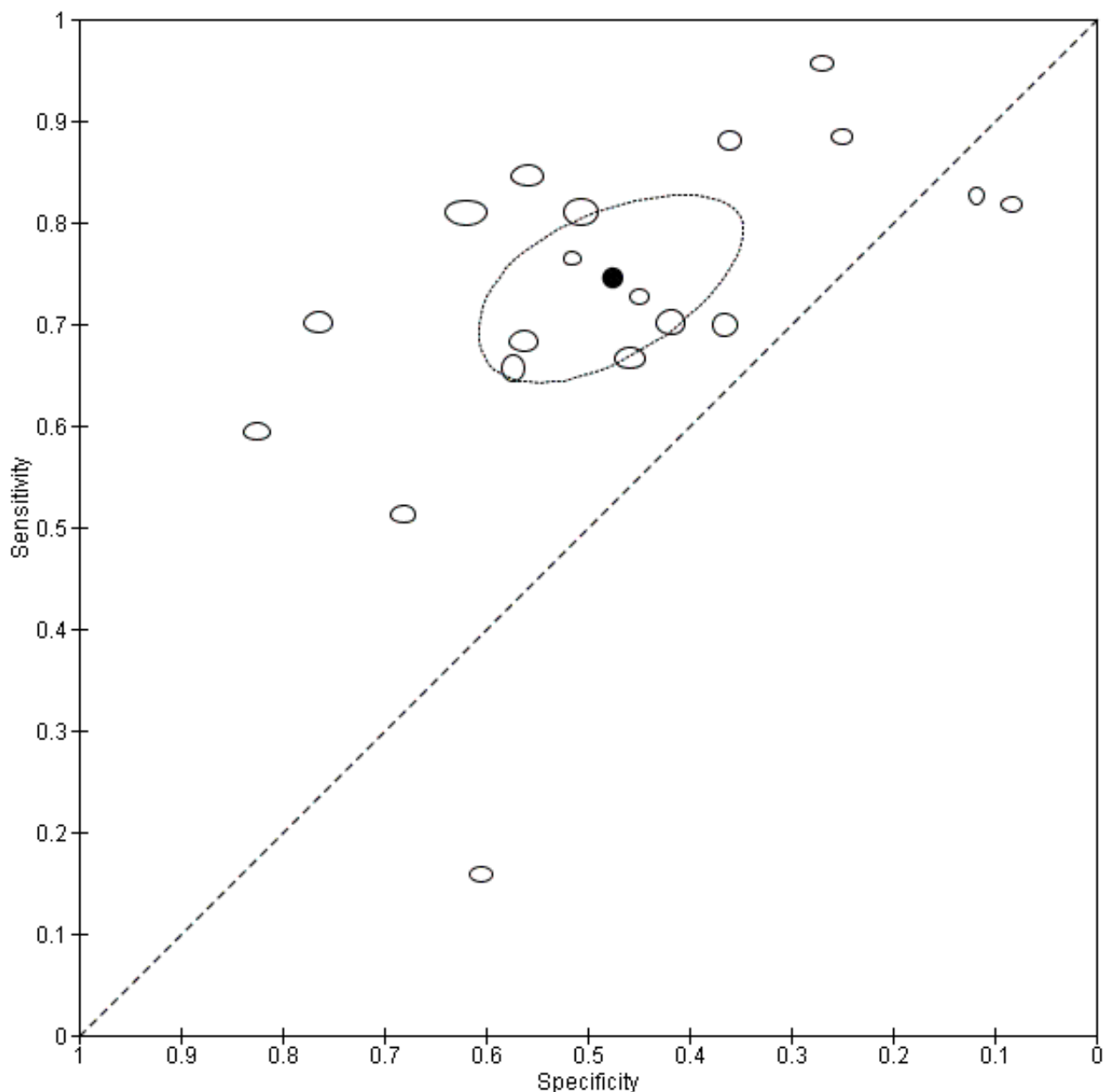
Only one study reported data according to renal units ([Sorkhi 2011](#)). This study found a sensitivity and specificity value of 0.30 and 0.84 in detecting VUR, respectively ([Data table 3](#)). The corresponding values for high-grade VUR were 0.29 and 0.81 ([Data table 4](#)).

DMSA

Nineteen studies reported data on the accuracy of DMSA in detecting VUR. The summary sensitivity and specificity estimates were 0.75 (95% CI 0.67 to 0.81) and 0.48 (95% CI 0.38 to 0.57), respectively ([Figure 6](#)). However, substantial heterogeneity between the accuracy values limits our confidence in these summary estimates ([Data table 5](#)). Nevertheless, no study reported

a specificity value close to 90%. Exclusion of children with a previous UTI explained some of the heterogeneity between estimates; the specificity of DMSA in studies of children with a first UTI (0.52, 95% CI 0.42 to 0.62) was higher ($P = 0.031$) than in studies in which children with > 1 UTI were included (0.24, 95% CI 0.11 to 0.47). Inclusion of afebrile children was another factor that explained some of the heterogeneity between studies; the sensitivity of DMSA in studies that included only febrile children (0.72, 95% CI 0.64 to 0.78) was lower ($P = 0.037$) than in studies which included afebrile children (0.88, 95% CI 0.74 to 0.95). Sensitivity analysis did not substantively alter the summary estimates.

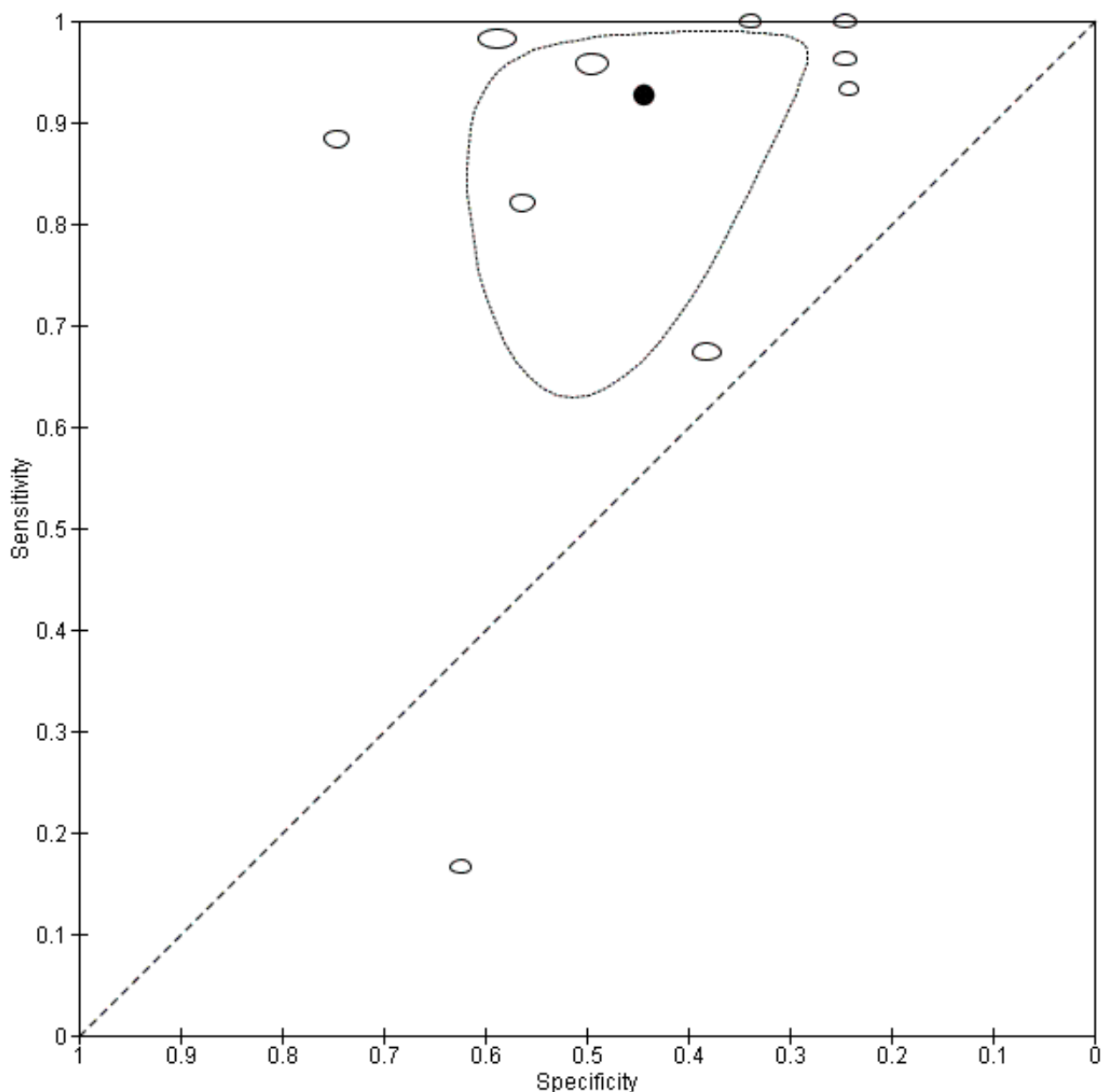
Figure 6. DMSA to detect VUR (all grades)



Ten studies reported data on the accuracy of DMSA in detecting high-grade VUR. The summary sensitivity and specificity estimates were 0.93 (95% CI 0.77 to 0.98) and 0.44 (95% CI 0.33 to 0.56), respectively (Figure 7). However, substantial heterogeneity between the specificity values limits our confidence in these summary measures (Data table 6). Two studies (Agras 2007; Hoberman 2003) reported sensitivity values that were clearly lower than the rest of the studies. The inclusion of afebrile children

explained some of the heterogeneity in the specificity values; the specificity of the DMSA scan in studies which included only febrile children (0.52, 95% CI 0.40 to 0.64; $P = 0.026$) was higher ($p = 0.026$) than in studies which included afebrile children (0.27, 95% CI 0.15 to 0.45). Limiting the analysis to low risk of bias studies did not substantively alter the summary estimate; limiting the analysis to studies with no applicability concerns resulted in slightly lower specificity values (0.34, 95% CI 0.26 to 0.43).

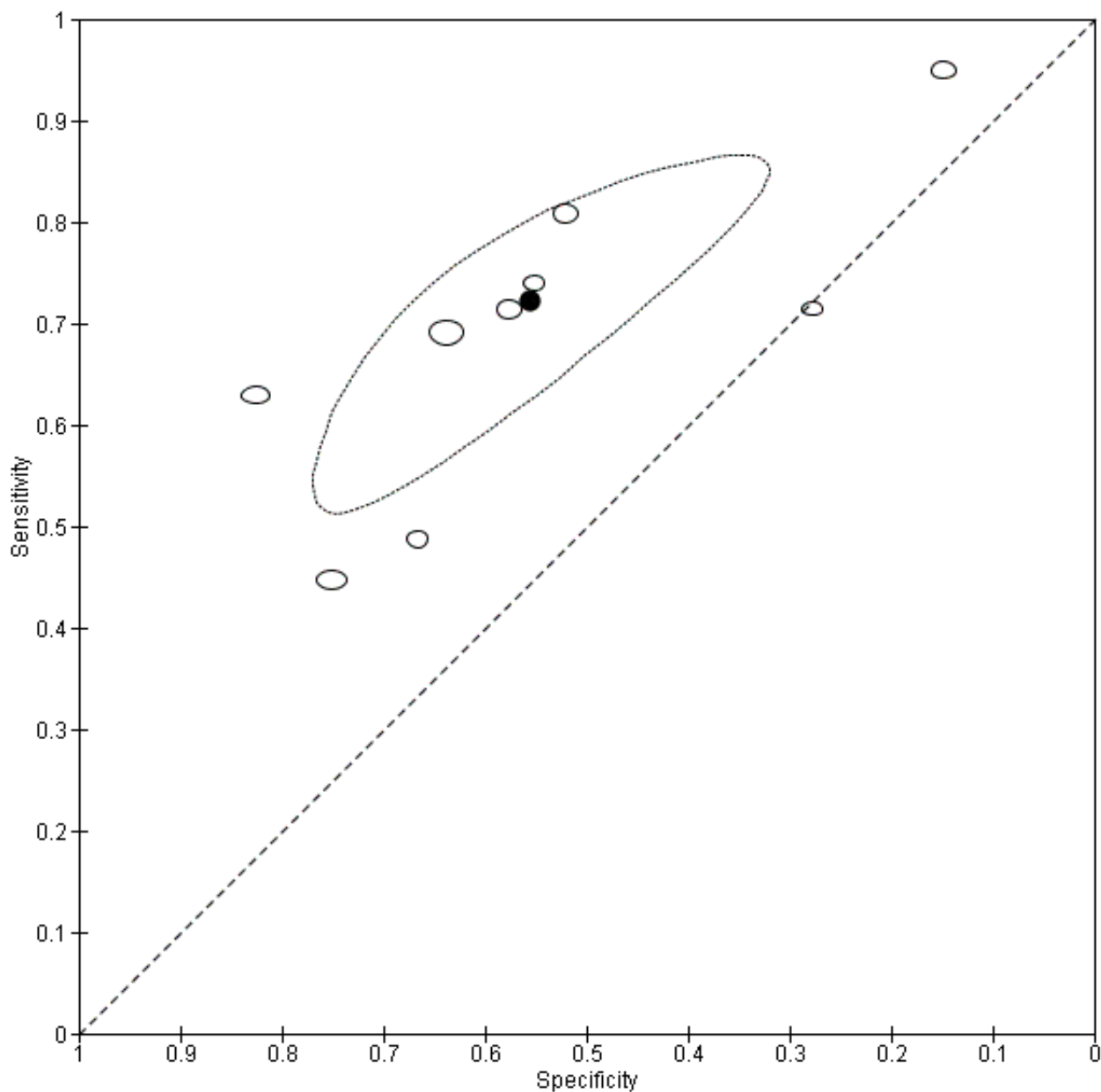
Figure 7. DMSA to detect high-grade VUR



Nine studies reported data regarding the accuracy of DMSA in predicting VUR according to renal units. The summary sensitivity and specificity estimates were 0.72 (95% CI 0.59 to 0.82) and 0.56 (95% CI 0.40 to 0.40), respectively (Figure 8). However, substantial heterogeneity between the accuracy values limits our confidence in the summary accuracy measures (Data table 7). Because of the small number of studies, meta-regression could not be performed

for the covariate relating to the use of paediatric urine collection bags. The inclusion of children with previous UTIs or the inclusion of afebrile children did not explain a significant proportion of the heterogeneity. Limiting the analysis to studies at high risk of bias or with concerns regarding applicability resulted in significantly lower specificity values (0.48, 95% CI 0.33 to 0.63).

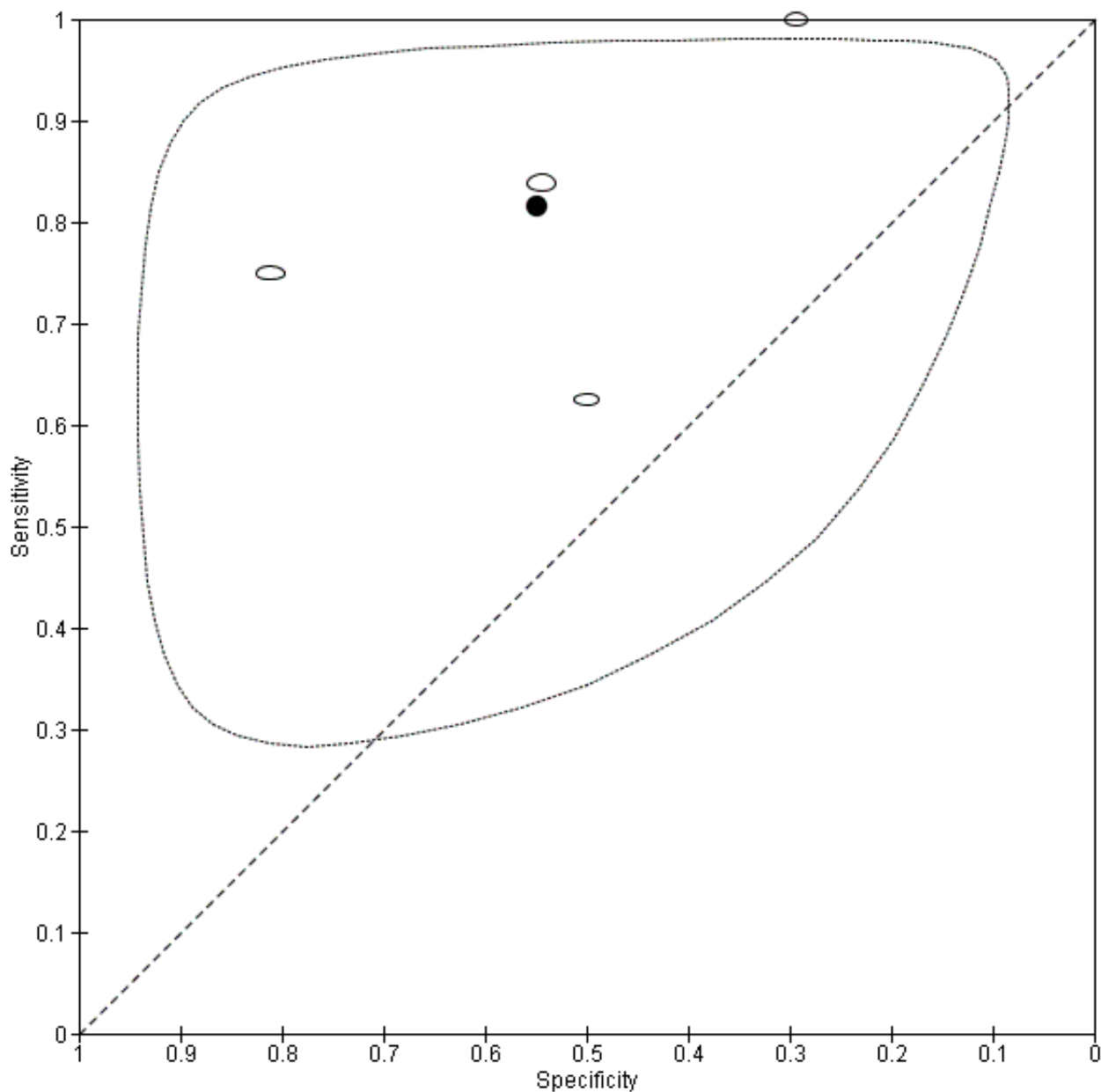
Figure 8. DMSA to detect renal units with VUR (all grades)



Four studies reported data regarding the accuracy of DMSA in predicting high-grade VUR according to renal units. The summary sensitivity and specificity estimates were 0.82 (95% CI 0.67 to

0.91) and 0.55 (95% CI 0.35 to 0.74), respectively (Figure 9). Meta-regression and sensitivity analysis were limited due to the small number of studies.

Figure 9. DMSA to detect renal units with high-grade VUR



Indirect comparison

Based on the available data (19 studies for DMSA and 20 studies for ultrasound), there was strong evidence ($P < 0.001$ for both) that DMSA had a higher sensitivity and lower specificity than ultrasound

for detecting VUR (Figure 10). Similarly, there was strong evidence ($P < 0.001$ for both) that DMSA had a higher sensitivity and lower specificity than ultrasound for detecting high-grade VUR (Figure 11).

Figure 10. Ultrasound versus DMSA for the detection of VUR (indirect comparison)

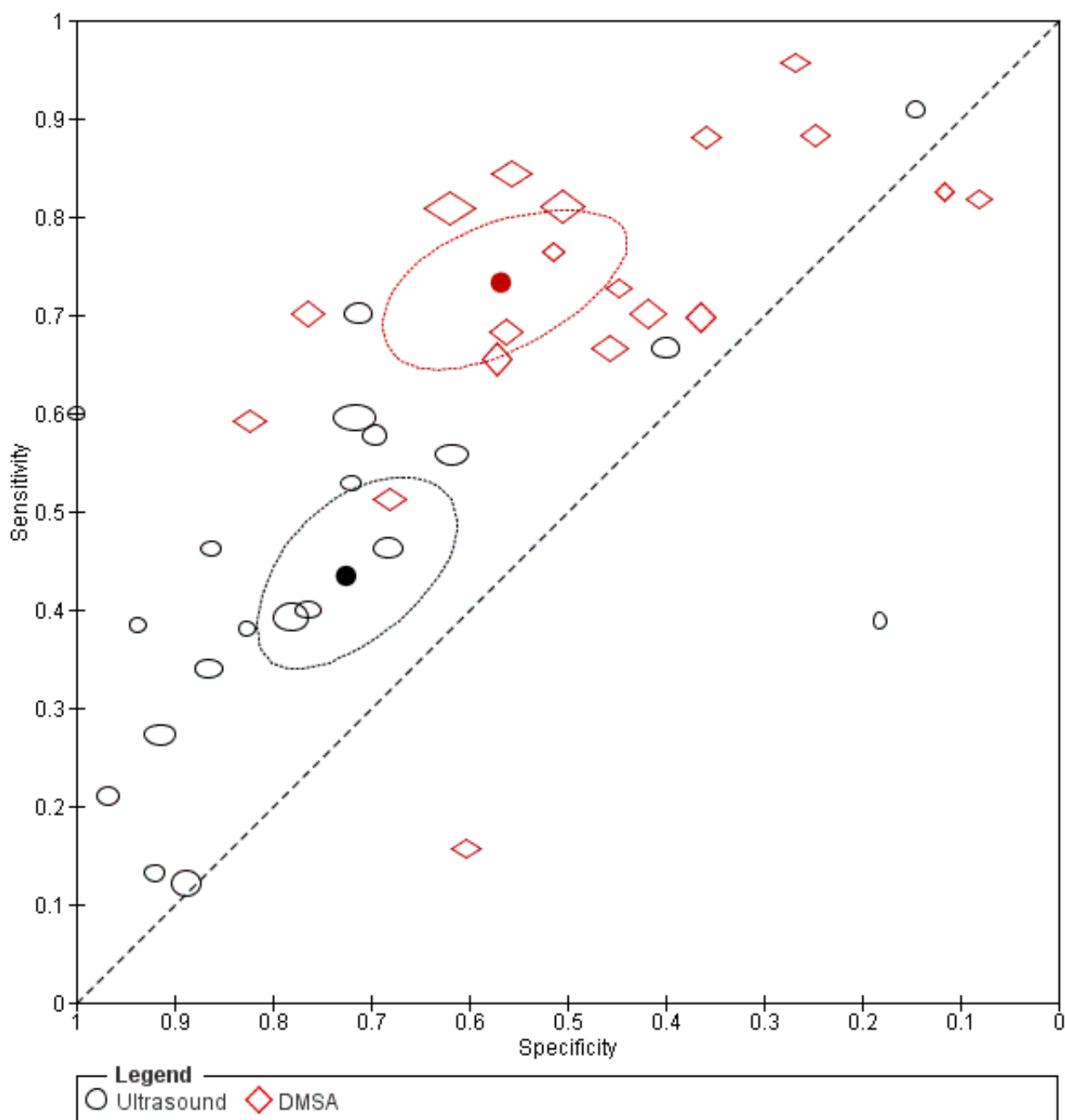
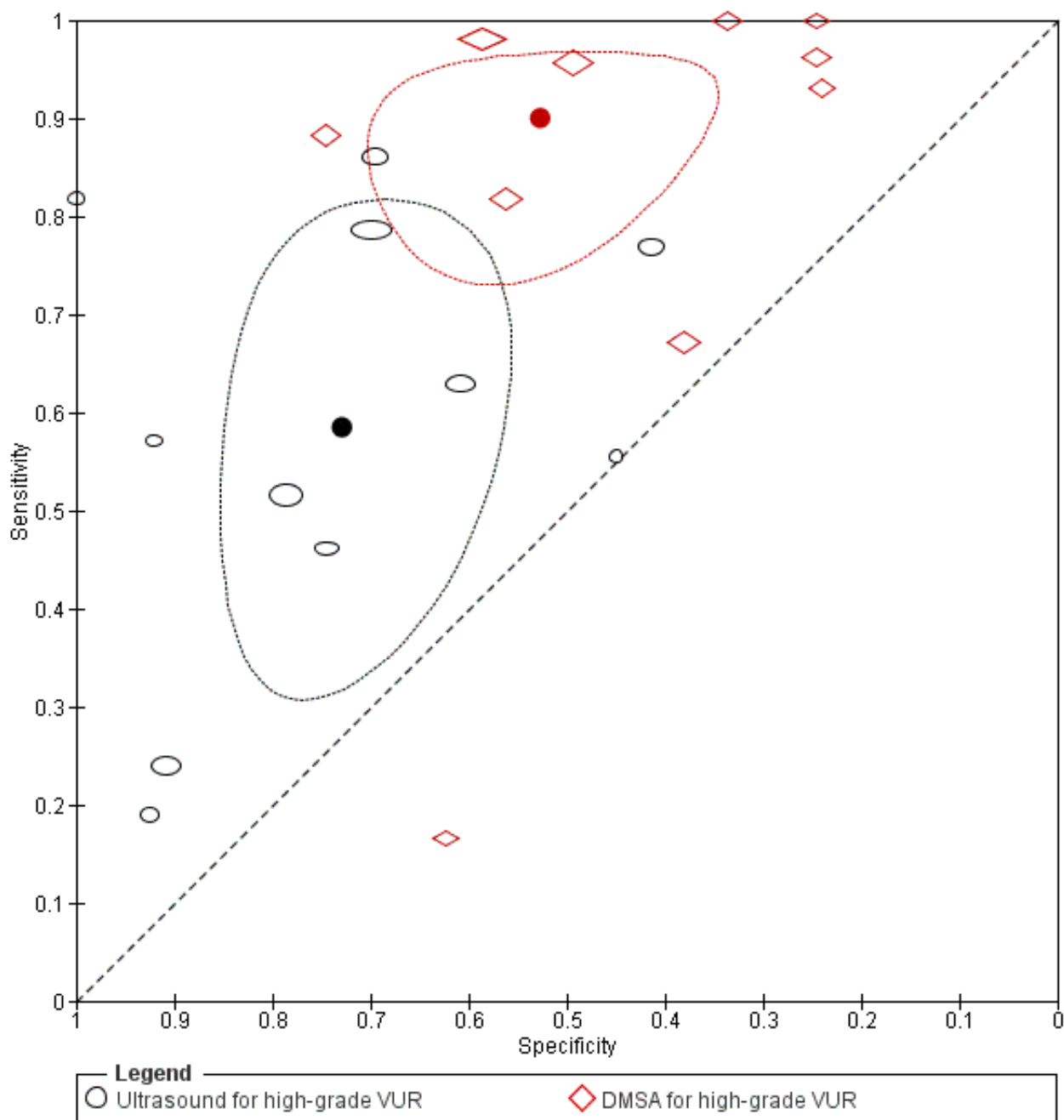


Figure 11. Ultrasound versus DMSA for the detection of High-Grade VUR (indirect comparison)

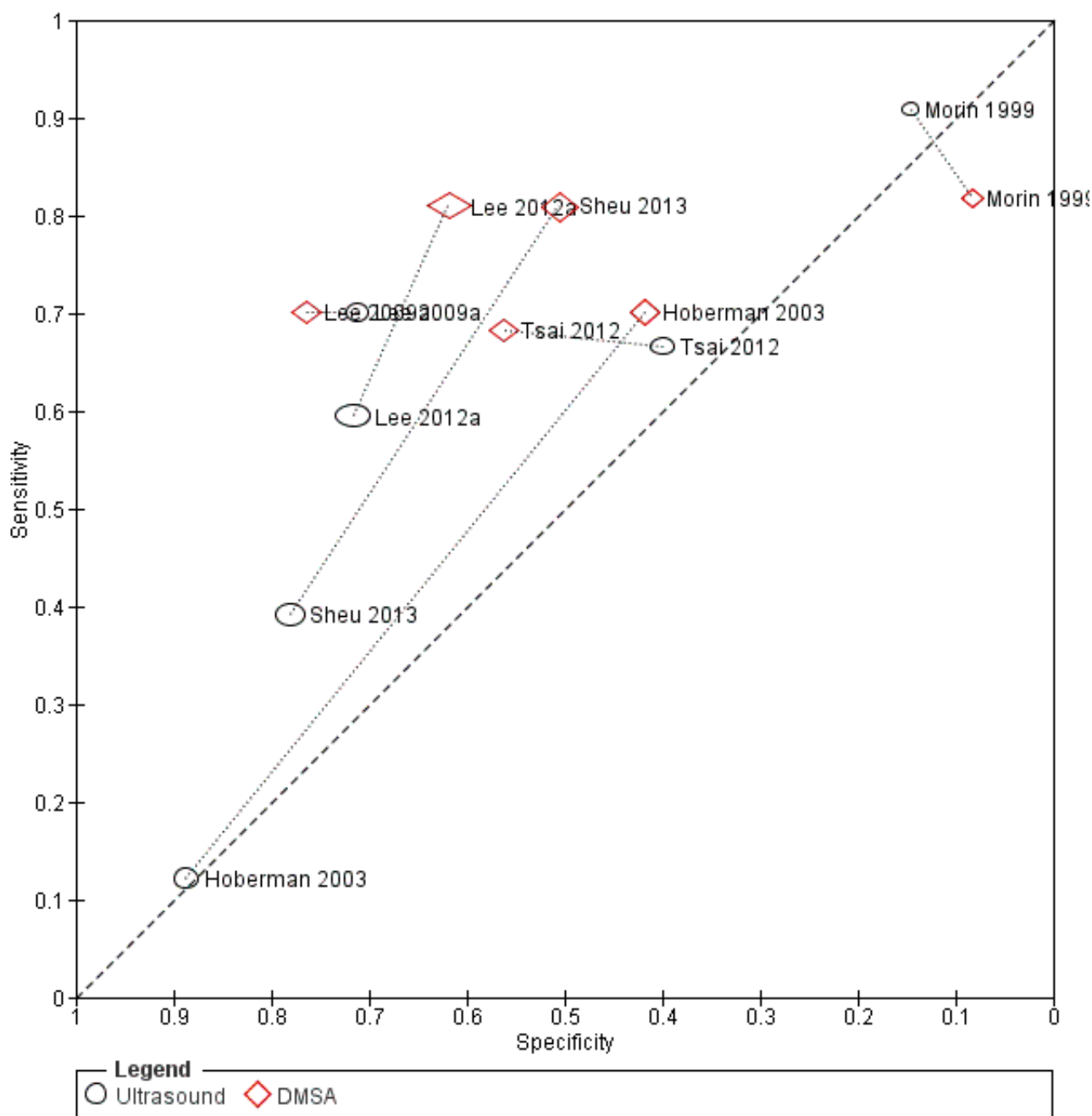


Direct comparison

Six studies provided data that allowed us to directly compare the DMSA and RBUS tests in detecting VUR (Figure 12). No clear pattern

was visible (three studies showed that the DMSA was more sensitive and less specific, but three other studies showed other results). Quantitative direct comparison was not possible.

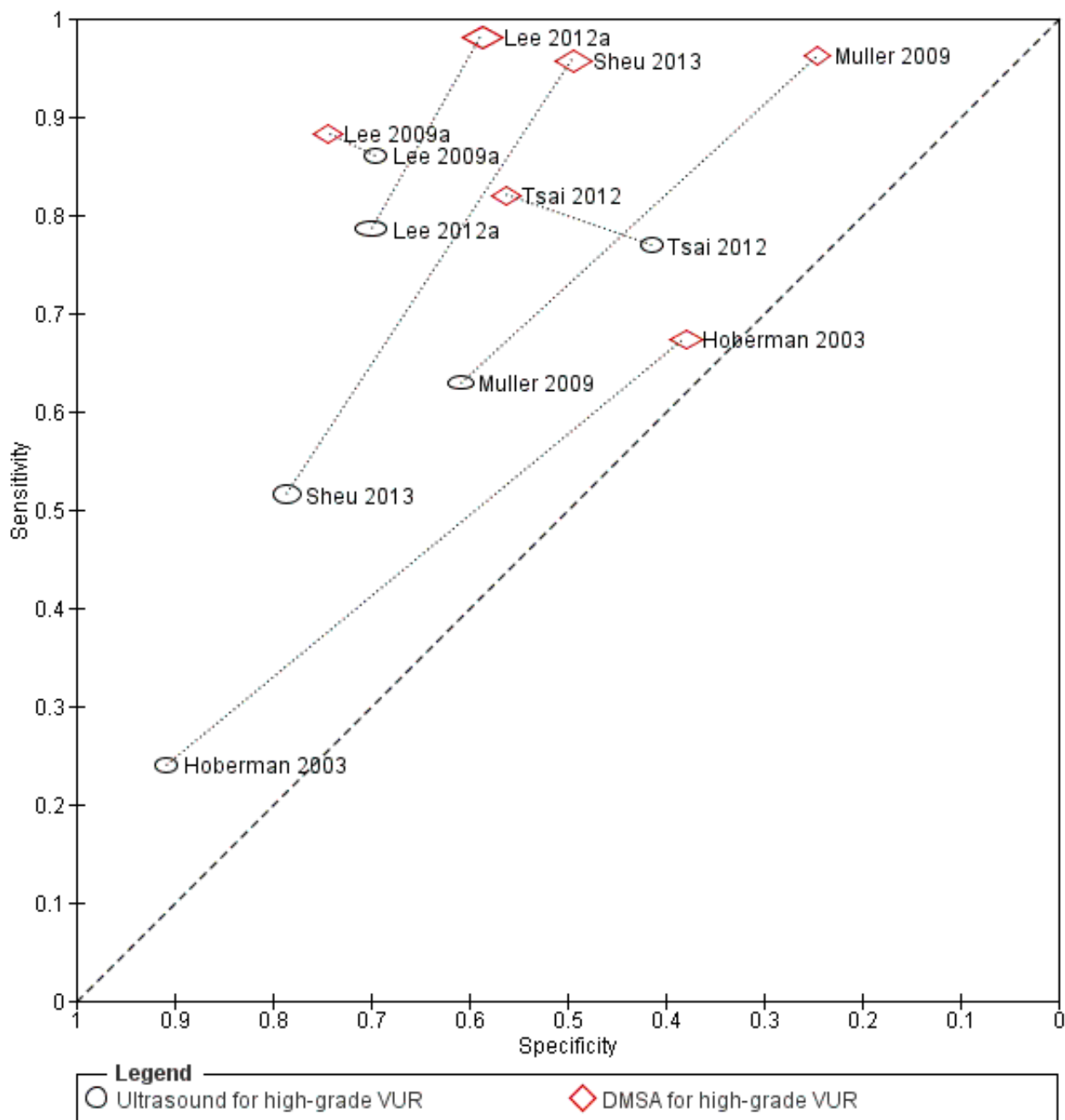
Figure 12. Direct comparison of ultrasound and DMSA tests in detecting VUR



Six studies provided data that allowed us to directly compare the DMSA and RBUS tests in detecting high-grade VUR (Figure 13). Four studies showed that the DMSA was more sensitive and less

specific than RBUS in detecting high-grade VUR. Quantitative direct comparison was not possible.

Figure 13. Direct comparison of ultrasound and DMSA in detecting high-grade VUR



Adverse events

We did not find any information on the incidence of adverse events related to the performance of RBUS or DMSA.

DISCUSSION

Summary of main results

In this review, we examined the accuracy of ultrasound and DMSA tests in diagnosing VUR and high-grade VUR.

We found that the ultrasound tests lack the accuracy to detect either VUR or high-grade VUR ([Summary of findings 1](#); [Summary of findings 2](#)), summary sensitivity values ranged from 0.44 to 0.59 and summary specificity values ranged from 0.78 to 0.79). Thus, the ultrasound test cannot replace the VCUG in detecting VUR. Nor can it serve to rule in or rule out VUR or high-grade VUR.

With regards to the DMSA test, examination of the scatter plots in ROC space reveals that despite the heterogeneity present, none of studies had accuracy values that were close to the top left hand corner of the ROC space. Thus, we can conclude that the DMSA

cannot replace the VCUG in the detection of VUR or high-grade VUR. The data from articles that reported data in terms of renal units was generally consistent with this conclusion. In particular, we found that the DMSA lacks specificity to detect either VUR or high-grade VUR ([Summary of findings 1](#); [Summary of findings 2](#), summary specificity values ranged from 0.44 to 0.58). Therefore, it is not a useful test to rule in VUR or high-grade VUR. The sensitivity of the DMSA for detecting VUR was intermediate ([Summary of findings 1](#), summary sensitivity value of 0.75), which limits its usefulness in ruling out VUR. The probability of VUR in a child with a positive DMSA is only 49%.

Because of its high sensitivity ([Summary of findings 2](#), summary sensitivity of 0.93), a negative DMSA test appears, at first glance, to be useful for ruling out high-grade VUR. In an average risk population of children with UTIs, a child with a negative DMSA test has a < 1% probability of having high-grade VUR. However, the low specificity of the test cannot be ignored. In average risk population of children with febrile UTIs, the DMSA test will be positive in approximately 70% patients. Accordingly, most children with UTI may be inappropriately labelled as high risk and undergo additional testing. Other practical considerations also limit the usefulness of the DMSA as a screening test including: 1) it requires an additional trip to the hospital, 2) it necessitates placement of an intravenous line, 3) it may require sedation, 4) it incurs an additional cost, 5) it requires specialized equipment and personnel, which may not be available locally, 6) its results are not available at the time of UTI diagnosis, 7) differentiation of old scars from pyelonephritis may be difficult in children with previous UTIs or dysplasia, and 8) it exposes children to radiation. Thus, although the sensitivity of the acute-phase DMSA for high-grade VUR is high, we do not find any compelling evidence to recommend its routine use as a screening test for VUR or high-grade VUR.

Strengths and weaknesses of the review

Unexplained heterogeneity among studies was a limitation that reduced our confidence in the summary accuracy estimates. Nevertheless, examination of the scatter plots enabled us to reach firm conclusions regarding the utility of the tests in clinical practice.

Applicability of findings to the review question

We did not find any compelling evidence to recommend the routine use of RBUS or DMSA as a screening test for VUR or high-grade VUR.

AUTHORS' CONCLUSIONS

Implications for practice

Although the sensitivity of the acute-phase DMSA for the detection of high-grade VUR is high, we do not find any compelling evidence to recommend this test as a screening test for high-grade VUR because of the limitations discussed above.

Implications for research

Given the limitations of the RBUS and DMSA in detecting VUR, and given that the VCUG test itself is invasive, future studies should focus on the identification of biomarkers that could identify the small minority of children with UTI who need closer follow-up. Future studies should utilize representative populations, avoid the use of bag samples, and present results stratified by age. Since accuracy is best studied in populations suspected of having the target condition, studies should be limited to febrile children.

ACKNOWLEDGEMENTS

We wish to acknowledge the support of the Cochrane Collaboration's Diagnostic Test Accuracy editorial team and the peer referees for their assistance.

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Shaikh N, Craig JC, Rovers MM, Da Dalt L, Gardikis S, Hoberman A, et al. Identification of children and adolescents at risk for renal scarring after a first urinary tract infection: a meta-analysis with individual patient data. *JAMA Pediatrics* 2014;**168**(10):893-900. [MEDLINE: 25089634]

Whiting 2011

Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine* 2011;**155**(8):529-36. [MEDLINE: 22007046]

References to other published versions of this review

Spingarn 2013

Spingarn RB, Shaikh N. Dimercaptosuccinic acid scan versus ultrasound in screening for vesicoureteral reflux among children with urinary tract infections. *Cochrane Database of Systematic Reviews* 2013, Issue 7. [DOI: [10.1002/14651858.CD010657](https://doi.org/10.1002/14651858.CD010657)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Agras 2007

Study characteristics			
Patient sampling	Prospective		
Patient characteristics and setting	217 children aged 2 months to 11 years with pyelonephritis who were hospitalised and had increased ESR/CRP and did not have a recurrent UTI during follow-up		
Index tests	DMSA		
Target condition and reference standard(s)	VUR, VCUG		
Flow and timing	DMSA was obtained within first week of fever and VCUG 6 to 8 weeks after APN		
Comparative			
Notes	Males > females, age up to 11 years		
Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		

Agras 2007 (Continued)

Did the study avoid inappropriate exclusions?	Yes		
		Low	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Alon 1986

Study characteristics			
Patient sampling	Prospective		
Patient characteristics and setting	81 children aged 12 weeks to 12 years with UTI who were hospitalised or seen at the outpatient clinic with symptomatic UTI; radiologic evaluation was indicated as per standard of care at the time		
Index tests	US		
Target condition and reference standard(s)	VUR, VCUG		
Flow and timing	US was performed within 4 days of hospitalisation and VCUG within 4 to 6 weeks after of completing antibiotics		
Comparative			
Notes			

Alon 1986 (Continued)

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Alon 1999
Study characteristics

Patient sampling	Retrospective study of patients with complete radiological evaluation
Patient characteristics and setting	100 children aged 1 month to 18 years admitted for a first febrile UTI or APN

Alon 1999 (Continued)

Index tests	US
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	US done during hospitalisation and VCUG 4 to 6 weeks after acute infection; 100/124 received VCUG
Comparative	
Notes	Only "major" ultrasound abnormalities considered

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
		High	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Ansari Gilani 2010
Study characteristics

Patient sampling	Prospective
Patient characteristics and setting	119 children aged 1 to 120 months with first UTI; setting not specified
Index tests	DMSA
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	All had DMSA within 1 week and 71/119 VCUG 4 weeks after admission
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			

Ansari Gilani 2010 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
High	

Ataei 2005

Study characteristics			
Patient sampling	Prospective		
Patient characteristics and setting	52 children aged 5 to 12 years (restricted age range) admitted to the hospital with suspected pyelonephritis and a high CRP who were admitted to hospital		
Index tests	DMSA		
Target condition and reference standard(s)	VUR, VCUG		
Flow and timing	DMSA was done within days of admission and VCUG within 5 to 7 days of admission		
Comparative			
Notes			
Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		High	Low

Ataei 2005 (Continued)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
	Low
	Low

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
	Low

Ataei 2008
Study characteristics

Patient sampling	Prospective
Patient characteristics and setting	102 patients aged 1 month to 12 years admitted to the hospital with high suspicion of pyelonephritis and a high CRP/ESR
Index tests	DMSA
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	DMSA within first days after admission, VCUG within 5 to 7 days of hospitalisation but before patient was discharged. 98/102 patients included in the analysis
Comparative	
Notes	Results in terms of renal units

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Ataei 2008 (Continued)

	Low	High
DOMAIN 2: Index Test All tests		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
	Low	Low
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear	
	Low	Low
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
	Low	

Calisti 2005

Study characteristics			
Patient sampling	Prospective		
Patient characteristics and setting	147 patients aged 1 to 24 months admitted with a first UTI		
Index tests	US		
Target condition and reference standard(s)	VUR, VCUG		
Flow and timing	Unclear timing of US and VCUG		
Comparative			
Notes			
Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns

Calisti 2005 (Continued)

DOMAIN 1: Patient Selection

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
	Low
	Low

DOMAIN 2: Index Test All tests

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear
	Low
	Low

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
	Low
	Low

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
	Low

Camacho 2004
Study characteristics

Patient sampling	Prospective
Patient characteristics and setting	142 children aged 1 month to 12 years with a first episode of febrile UTI; setting not specified
Index tests	DMSA
Target condition and reference standard(s)	VUR, VCUG

Camacho 2004 (Continued)

Flow and timing

DMSA within 5 days of presentation and VCUG after acute phase of illness

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Cascio 2002
Study characteristics

Patient sampling	Retrospective study of patients with complete radiological evaluation
Patient characteristics and setting	57 children aged 0 to 8 weeks hospitalised with a first UTI
Index tests	DMSA
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	DMSA within 72 hours of admission and VCUG at least 6 weeks after UTI
Comparative	
Notes	Data in terms of renal units, DMSA threshold not specified

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
		High	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		

Cascio 2002 (Continued)

Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Low	

Cleper 2004
Study characteristics

Patient sampling	Retrospective study of patients admitted or referred to paediatric nephrology clinic with diagnosis of neonatal UTI or sepsis work-up and who had complete radiological evaluation
Patient characteristics and setting	64 neonates aged 0 to 1 month of age with UTI
Index tests	US
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	US on admission, VCUG 3 to 4 weeks after acute infection
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
		High	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Cleper 2004 (Continued)

Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear

Low
Low
DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard? Yes

Did all patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

Low
Doganis 2007
Study characteristics

Patient sampling Prospective

Patient characteristics and setting 278 infants aged < 12 months with first febrile UTI who were admitted to the hospital; males > females

Index tests DMSA

Target condition and reference standard(s) VUR, VCUG

Flow and timing DMSA within 18 days of admission and VCUG before discharge; 9 parents refused VCUG (269/278 had complete data)

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
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DOMAIN 1: Patient Selection

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Low
Low
DOMAIN 2: Index Test All tests

Doganis 2007 (Continued)

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		Low	

Donoso 2004

Study characteristics			
Patient sampling	Prospective		
Patient characteristics and setting	143 children with a first episode of pyelonephritis; unclear whether elevated CRP/EST or peripheral WBC count was used for inclusion; unclear whether children were "referred" for DMSA scan or whether this was per protocol		
Index tests	DMSA		
Target condition and reference standard(s)	VUR, VCUG		
Flow and timing	DMSA was done within 7 days of diagnosis and VCUG unspecified (69% within the first month); 127/143 with complete data		
Comparative			
Notes			
Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns

Donoso 2004 (Continued)

DOMAIN 1: Patient Selection

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
	Low Unclear

DOMAIN 2: Index Test All tests

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
	Low Low

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
	Low Low

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
	Low

El Shenoufy 2009
Study characteristics

Patient sampling	Prospective
Patient characteristics and setting	45 children aged 1 to 5 years with symptoms of UTI referred to the "Pediatric Outpatient and Urology clinic at Pediatric Specialized Hospital"
Index tests	US
Target condition and reference standard(s)	VUR, VCUG

El Shenoufy 2009 (Continued)

Flow and timing

US a week from acute infection and VCUG 4 to 6 weeks after the onset of infection

Comparative

Notes

Threshold for US not clear

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Fernandez-Menendez 2003
Study characteristics

Patient sampling	Prospective
Patient characteristics and setting	158 children aged 1 month to 14 years with a first episode of symptomatic UTI (85% < 2 years); patients attended the emergency room and were then admitted to the hospital; all but 5 had fever
Index tests	DMSA
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	DMSA within 10 days, VCUG within 4 weeks after diagnosis; 150/158 with complete data
Comparative	
Notes	Data in terms of renal units, older age not typical

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			

Fernandez-Menendez 2003 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Low	

Goldman 2000

Study characteristics			
Patient sampling	Prospective		
Patient characteristics and setting	45 male neonates aged 0 to 2 months hospitalised with a UTI		
Index tests	US		
Target condition and reference standard(s)	VUR, VCUG		
Flow and timing	US in the acute phase and VCUG 4 to 6 weeks after the diagnosis; 1 did not receive VCUG		
Comparative			
Notes	US threshold not specified		
Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			

Goldman 2000 (Continued)

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
	Low
	Low
DOMAIN 4: Flow and Timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
	Low

Hoberman 2003

Study characteristics			
Patient sampling	Prospective		
Patient characteristics and setting	309 children aged 1 to 24 months admitted with first febrile UTI		
Index tests	US and DMSA		
Target condition and reference standard(s)	VUR, VCUG		
Flow and timing	US within 48 hours of diagnosis, DMSA within 48 hours of diagnosis in all and VCUG 1 month after diagnosis in 302/309		
Comparative			
Notes	5 children with abnormal ultrasound but no dilation not included in the analysis for US (i.e., threshold for US was dilation)		
Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low

Hoberman 2003 (Continued)

DOMAIN 2: Index Test All tests

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
	Low
	Low

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
	Low
	Low

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
	Low

Ilyas 2002
Study characteristics

Patient sampling	Retrospective study of patients with complete radiological evaluation
Patient characteristics and setting	222 children aged 2 months to 19 years old admitted to hospital with UTI
Index tests	DMSA
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	DMSA within 48 hours of admission and VCUG within 6 weeks of diagnosis; 14/222 patients don't have VCUG data
Comparative	
Notes	SPECT DMSA used

Methodological quality

Ilyas 2002 (Continued)

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		Low	

Ismaili 2011

Study characteristics	
Patient sampling	Prospective
Patient characteristics and setting	209 children aged 0.2 to 204 months with first febrile UTI and increased CRP and/or ESR evaluated at the emergency department; did not exclude patients with known renal or genitourinary abnormalities

Ismaili 2011 (Continued)

Index tests	US
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	US within 48 hours of diagnosis and VCUG at least 1 month after UTI
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Jakobsson 1992
Study characteristics

Patient sampling	Prospective
Patient characteristics and setting	106 children aged 0 to 15.9 years (median 0.7 years) with symptomatic UTI who were admitted to hospital
Index tests	DMSA
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	DMSA within 5 days and VCUG 2 months after infection as late as 20 weeks
Comparative	
Notes	Urine culture definition obtained from other studies by the same author

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			

Jakobsson 1992 (Continued)

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Low	

Kim 2006

Study characteristics			
Patient sampling	Retrospective		
Patient characteristics and setting	Sample of 52 children with a first febrile UTI; high proportion of patients with Grade IV VUR		
Index tests	US		
Target condition and reference standard(s)			
Flow and timing	US within 72 hours and VCUG 1 to 4 weeks after index UTI		
Comparative			
Notes	Limited translation from Korean; threshold for US unclear		
Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
		Low	Low
DOMAIN 3: Reference Standard			

Kim 2006 (Continued)

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
	Low
	Low
DOMAIN 4: Flow and Timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
	Low

Lavocat 1997

Study characteristics	
Patient sampling	Prospective
Patient characteristics and setting	55 children aged 15 days to 15.5 years admitted for first UTI with a CRP > 20 mg/L
Index tests	DMSA
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	DMSA within 2 weeks; VCUG a minimum of 3 weeks after onset of UTI
Comparative	
Notes	Data in terms of renal units, 3 patients with change in renal contour or small renal volume on DMSA not counted as abnormal

Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	High

Lavocat 1997 (Continued)

DOMAIN 2: Index Test All tests

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
	Low
	Low

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
	Low
	Low

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
	Low

Lee 2009a
Study characteristics

Patient sampling	Retrospective; appears that only patients with complete imaging evaluation were included
Patient characteristics and setting	220 children aged 0 to 2 years with first febrile UTI; setting not specified; males > females
Index tests	US and DMSA
Target condition and reference standard(s)	VUR, VCUG; DMSA threshold unusual: > 1 area of photopenia (instead of ≥ 1)
Flow and timing	US immediately after diagnosis, DMSA/VCUG after resolution of fever and confirmation of culture results
Comparative	
Notes	

Methodological quality

Lee 2009a (Continued)

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	Low
DOMAIN 2: Index Test Ultrasound			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 2: Index Test DMSA			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		High	High
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Lee 2012a
Study characteristics

Patient sampling	Retrospective study of patients with complete radiological evaluation
Patient characteristics and setting	618 children aged 0 to 12 years old admitted to the hospital with first febrile UTI and CRP > 0.3 mg/dL
Index tests	US and DMSA
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	US/DMSA within 4 days of admission, VCUG within 2 weeks of resolution of fever
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			

Lee 2012a (Continued)

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Low	

Lin 2007

Study characteristics			
Patient sampling	Retrospective. Imaging appears to have been per protocol (standard of care).		
Patient characteristics and setting	114 children aged 0 to 1 years diagnosed with first documented UTI with fever or non-specific clinical manifestation; setting not specified; males > females		
Index tests	DMSA		
Target condition and reference standard(s)	VUR, VCUG		
Flow and timing	DMSA within 3 days of admission; VCUG after resolution of fever		
Comparative			
Notes	Renal units data		
Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low

Lin 2007 (Continued)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
	Low

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
	Low

Lopez Sastre 2007
Study characteristics

Patient sampling	Prospective
Patient characteristics and setting	301 infants aged 4 to 40 days old with UTI admitted to acute-care teaching hospitals
Index tests	US
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	US/VCUG after infectious episode; 291/301 underwent US and 262/301 underwent VCUG
Comparative	
Notes	Nosocomial UTI in study but we excluded these patients from our analysis; although threshold for US not clear, most patients had dilatation

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		

Lopez Sastre 2007 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
		Low	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	No		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		Low	

Mahant 2002

Study characteristics			
Patient sampling	Retrospective		
Patient characteristics and setting	170 children aged < 5 years with a first UTI who were admitted to the hospital		
Index tests	US		
Target condition and reference standard(s)	VUR, VCUG		
Flow and timing	US was performed during admission (mean 2 days); unclear timing for VCUG; VCUG not performed in 8/70		
Comparative			
Notes			

Mahant 2002 (Continued)

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		Low	

Melis 1992
Study characteristics

Patient sampling	Retrospective; imaging was per hospital protocol
Patient characteristics and setting	146 patients < 16 years admitted with a febrile UTI; 47% < 2 years; did not exclude children with previous genitourinary/renal abnormalities

Melis 1992 (Continued)

Index tests	US
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	US within 1 week of UTI; VCUG 3 to 6 weeks; 99/146 had VCUG
Comparative	
Notes	Data according to renal units; did not exclude children with previous genitourinary/renal anomalies

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		
		High	

Montini 2009
Study characteristics

Patient sampling	Prospective
Patient characteristics and setting	300 children aged 1 month to 2 years with a first febrile UTI and an elevated CRP and/or neutrophil count and who had all imaging tests and a 12 month follow-up; patients from 28 paediatric units in northeast Italy
Index tests	US
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	US within 10 days, VCUG within 2 months; 17/438 had missing US/VCUG; 63/363 patients excluded based on missing 12 month DMSA
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	Low
DOMAIN 4: Flow and Timing			

Montini 2009 (Continued)

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Low	

Morin 1999
Study characteristics

Patient sampling	Prospective
Patient characteristics and setting	70 children aged 1 month to 17 years old admitted with first episode of pyelonephritis and an elevated CRP (> 20 mg/L)
Index tests	US and DMSA
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	US on admission, DMSA within 5 days of admission, and VCUG within 4 weeks
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			

Morin 1999 (Continued)

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
	Low
DOMAIN 4: Flow and Timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
	Low

Muller 2009

Study characteristics			
Patient sampling	Prospective		
Patient characteristics and setting	325 infants aged < 1 year with a first UTI diagnosed in the emergency department		
Index tests	US		
Target condition and reference standard(s)	VUR, VCUG		
Flow and timing	US within a week of diagnosis in 290/325; VCUG within 2 months in 313/325		
Comparative			
Notes			
Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low

Muller 2009 (Continued)

DOMAIN 2: Index Test All tests

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		Low	

Oh 2012
Study characteristics

Patient sampling	Prospective
Patient characteristics and setting	230 children admitted first febrile UTI; mean age 9 months; males > females
Index tests	DMSA
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	DMSA within 7 days; VCUG 3 to 6 weeks
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
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Oh 2012 (Continued)

DOMAIN 1: Patient Selection

Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low

DOMAIN 2: Index Test All tests

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Preda 2007

Study characteristics

Patient sampling	Prospective
Patient characteristics and setting	325 infants aged < 1 year with first symptomatic UTI diagnosed in the emergency department
Index tests	DMSA
Target condition and reference standard(s)	VUR, VCUG

Preda 2007 (Continued)

Flow and timing

DMSA < 30 days; VCUG within 2 months; excluded 11 with no VCUG and 24 with missing DMSA or DMSA conducted after 30 days

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		Low	

Sayedzadeh 2011
Study characteristics

Patient sampling	Cross-sectional; unclear whether all patients were included or only those with complete radiological studies
Patient characteristics and setting	40 children aged 1 month to 5 years with fever for more than 48 hours; high percentage of patients with VUR; setting not specified
Index tests	DMSA
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	DMSA within 14 days; VCUG after treatment and negative urine culture
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
		Unclear	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			

Sayedzadeh 2011 (Continued)

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Low	

Sheu 2013

Study characteristics			
Patient sampling	Prospective		
Patient characteristics and setting	473 children aged < 2 years old hospitalised with a first febrile UTI		
Index tests	US and DMSA		
Target condition and reference standard(s)	VUR, VCUG		
Flow and timing	US within 3 days, DMSA within 5 days, and VCUG within 1 month of UTI		
Comparative			
Notes			
Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			

Sheu 2013 (Continued)

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
	Low
	Low
DOMAIN 4: Flow and Timing	
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
	Low

Sorkhi 2011

Study characteristics			
Patient sampling	Prospective		
Patient characteristics and setting	100 children study of children referred to the research centre with first time episode of pyelonephritis; unspecified age		
Index tests	US and DMSA		
Target condition and reference standard(s)	VUR, VCUG		
Flow and timing	VCUG and DMSA within 5 days of diagnosis of UTI		
Comparative			
Notes	Data in terms of renal units; Table 2 data appear incorrect; used data in Table 3		
Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	High

Sorkhi 2011 (Continued)

DOMAIN 2: Index Test All tests

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Soylu 2007
Study characteristics

Patient sampling	Retrospective study of patients with complete radiological evaluation
Patient characteristics and setting	88 patient aged 0 to 204 months with febrile UTI who were referred to the Paediatric Nephrology Unit
Index tests	US
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	Unclear timing for US and VCUG
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
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Soylu 2007 (Continued)

DOMAIN 1: Patient Selection

Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	High

DOMAIN 2: Index Test All tests

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Supavekin 2013a
Study characteristics

Patient sampling	Prospective
Patient characteristics and setting	67 hospitalised children aged 0.02 to 7.26 years hospitalised with first episode of UTI; mean age of 1 year
Index tests	US
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	US timing unclear

Supavekin 2013a *(Continued)*

Comparative

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Tsai 1996
Study characteristics

Tsai 1996 (Continued)

Patient sampling	Retrospective study of patients with complete radiological evaluation
Patient characteristics and setting	247 children aged < 16 years admitted to the hospital for UTI
Index tests	DMSA
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	DMSA within first 3 days of diagnosis and VCUG 10 to 14 days after treatment; 230/247 had VCUG
Comparative	
Notes	Data according to renal units

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	High
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Tsai 1996 (Continued)

Were all patients included in the analysis?

No

Low
Tsai 2012
Study characteristics

Patient sampling	Prospective
Patient characteristics and setting	231 infants aged 0 to 3 months hospitalised with first febrile UTI
Index tests	US and DMSA
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	US within 3 days and DMSA within 5 days of diagnosis of UTI; VCUG 7 to 10 days after end of antibiotic therapy; 11/231 patients with missing DMSA or VCUG were excluded
Comparative	
Notes	Those with increased bladder wall thickness were counted as having an abnormal renal ultrasound

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	High
DOMAIN 2: Index Test Ultrasound			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	High
DOMAIN 2: Index Test DMSA			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

Tsai 2012 (Continued)

If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		Low	

Tseng 2007

Study characteristics			
Patient sampling	Retrospective study of patients with complete radiological evaluation		
Patient characteristics and setting	232 children aged < 2 years admitted with a first episode of UTI		
Index tests	DMSA		
Target condition and reference standard(s)	VUR, VCUG		
Flow and timing	DMSA 48 hours after diagnosis; VCUG 1 month after diagnosis; 90/232 patients with incomplete imaging evaluation excluded		
Comparative			
Notes			
Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		

Tseng 2007 (Continued)

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Zaki 1996

Study characteristics			
Patient sampling	Prospective		
Patient characteristics and setting	50 children aged 6 months to 12 years admitted with a first febrile UTI		
Index tests	DMSA		
Target condition and reference standard(s)	VUR, VCUG		
Flow and timing	DMSA within 1 week of admission; VCUG 2 to 4 weeks after presentation		
Comparative			

Zaki 1996 (Continued)

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Zaki 2003
Study characteristics

Patient sampling	Retrospective
Patient characteristics and setting	174 children aged 0 to 12 years admitted with first febrile UTI, high CRP (> 40 mg/L) and had DMSA and VCUG; however, DMSA was

Zaki 2003 (Continued)

standard of care and VCUG was only missing in 7 patients; exclusion based on ethnicity

Index tests	DMSA
Target condition and reference standard(s)	VUR, VCUG
Flow and timing	DMSA within 1 week of admission; VCUG at least 1 month after infection
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	High
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Zaki 2003 (Continued)

Low

APN - acute pyelonephritis; CRP - C-reactive protein; DMSA - ⁹⁹Tc-dimercaptosuccinic acid; ESR - erythrocyte sedimentation rate; SPECT - single-photon emission computed tomography; US - ultrasound; UTI - urinary tract infection; VCUG - voiding cystourethrography; VUR - vesicoureteric reflux; WBC - white blood cell

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adibi 2013	UTI definition not specified
Ahmadzadeh 2007	UTI definition not met
Ajdinovic 2005	DMSA timing not given
Ajdinovic 2006	DMSA timing not given
Ajdinovic 2008	DMSA performed later than 1 month
Ajdinovic 2010	Not enough data to calculate sensitivity/specificity
Aktas 2008	DMSA performed later than 1 month
Almeida 1994	UTI definition not met
Alshamsam 2009	UTI definition not met
Alvarez 2009	Not relevant
Alzen 1994	Not all patients had a UTI
Asanuma 2012	Not enough data to calculate sensitivity/specificity
Balbay 1998	UTI definition not specified
Barros 2010	VCUG only in high-risk children
Beiraghdar 2012	Not enough data to calculate sensitivity/specificity
Ben-Ami 1989	Not enough data to calculate sensitivity/specificity
Benador 1994	Not enough data to calculate sensitivity/specificity
Benador 1997	UTI definition not met
Benador 1998	UTI definition not met
Benador 2001	UTI definition not met
Bergius 1990	UTI definition not specified
Berry 2012	UTI definition not specified

Study	Reason for exclusion
Bhatnagar 2002	UTI definition not specified
Biggi 2001	Not enough data to calculate sensitivity/specificity
Biyikli 2004	Not enough data to calculate sensitivity/specificity
Blane 1993	Not all patients had a UTI
Boudailliez 1989	Gold standard was not radiographic VCUG
Bouissou 1988	Not enough data to calculate sensitivity/specificity
Bouissou 1994	DMSA performed later than 1 month
Butorac-Ahel 2011	Not enough data to calculate sensitivity/specificity
Cabezuelo Huerta 2005	UTI definition not specified
Caillaud 2013	Not enough data to calculate sensitivity/specificity
Calleja Gero 2008	Not enough data to calculate sensitivity/specificity
Castello Girona 1995	UTI definition not met
Cemerlic-Zececiv 2002	DMSA performed later than 1 month
Cheng 2011	Not enough data to calculate sensitivity/specificity
Chroustova 2006	DMSA performed later than 1 month
Clarke 1996	DMSA timing not given
Cortes 2010	Not enough data to calculate sensitivity/specificity
Craig 1998	UTI definition not met
D'Souza 2013	Enhanced ultrasound
David 1998	Not all patients had a UTI
De Mutiis 2011	Not enough data to calculate sensitivity/specificity
DiPietro 1997	UTI definition not specified
Ditchfield 1994	Index test is Tc-99gluconate, not DMSA
Ditchfield 1998	DMSA timing not given
Donoso 2012	DMSA performed later than 1 month
Dura Trave 1997	UTI definition not specified
Ekim 1992	Not enough data to calculate sensitivity/specificity
El-Naggari 2011	Not enough data to calculate sensitivity/specificity

Study	Reason for exclusion
Elison 1992	DMSA timing not given
Fallahzadeh 2008	UTI definition not specified
Farnsworth 1991	DMSA performed later than 1 month
Fidan 2013	Not enough data to calculate sensitivity/specificity
Foresman 2001	UTI definition not met
Fouzas 2010	Gold standard was not radiographic VCUG
Gelfand 2000	UTI definition not specified
Geronikola-Trapali 2010	Not enough data to calculate sensitivity/specificity
Ghiro 2002	UTI definition not met
Giorgi 2005	UTI definition not specified
Gomez Tellado 1994	Not enough data to calculate sensitivity/specificity
Gupta 2011	Not enough data to calculate sensitivity/specificity
Halevy 2013	Not enough data to calculate sensitivity/specificity
Hamoui 2008	Not enough data to calculate sensitivity/specificity
Hannula 2009	Not enough data to calculate sensitivity/specificity
Hannula 2010	Not enough data to calculate sensitivity/specificity
Hannula 2011	UTI definition not specified
Hansson 1997	Not enough data to calculate sensitivity/specificity
Hansson 2004	DMSA performed later than 1 month
Haznedaroglu 1996	UTI definition not specified
Herz 2005	Not enough data to calculate sensitivity/specificity
Herz 2010	UTI definition not specified
Hiraoka 1996	Not enough data to calculate sensitivity/specificity
Hiraoka 1997	Not enough data to calculate sensitivity/specificity
Honkinen 1986	Gold standard not radiographic VCUG
Huang 2008	UTI definition not met
Inoue 2011	Not enough data to calculate sensitivity/specificity
Jakobsson 1996	Not enough data to calculate sensitivity/specificity

Study	Reason for exclusion
Jakobsson 1997	UTI definition not specified
Jarmolinski 2011	Not enough data to calculate sensitivity/specificity
Jaukovic 2009	DMSA performed later than 1 month
Jequier 1985	UTI definition not specified
Jewkes 1990	UTI definition not specified
Johnson 1985	UTI definition not met
Johnson 1986	UTI definition not met
Juliano 2013	UTI definition not specified
Kanellopoulos 2005	Not enough data to calculate sensitivity/specificity
Kanellopoulos 2006	UTI definition not met
Kangaroo 1985	Not enough data to calculate sensitivity/specificity
Kaplan Bulut 2011	Not enough data to calculate sensitivity/specificity
Kass 1992	Index test is TC-glucoheptonate, not DMSA
Kass 2000	UTI definition not specified
Kim 2010	Not enough data to calculate sensitivity/specificity
Kljucevsek 2009	Enhanced ultrasound
Krzemien 2002	UTI definition not met
Kuzmanovska 2008	Gold standard was not radiographic VCUG
La Scola 2013	UTI definition not specified
Lee 2009b	Not all patients had a UTI
Lee 2012b	Not all patients had a UTI
Leroy 2010	Not enough data to calculate sensitivity/specificity
Lim 2010	UTI definition not specified
Lin 2003	Gold standard was not uniformly VCUG
Lytzen 2011	Not enough data to calculate sensitivity/specificity
MacLeod 2011	Not enough data to calculate sensitivity/specificity
Mage 1989	UTI definition not specified
Majd 1991	Gold standard was not uniformly VCUG

Study	Reason for exclusion
Martin Aguado 2000	Not enough data to calculate sensitivity/specificity
Martinez 2012	DMSA timing not given
Masalskiene 2011	UTI definition not specified
Massanyi 2013	Gold standard not radiographic VCUG
Matesanz 1998	Not all patients had UTI
Mazigh Mrad 2002	Not relevant (no VCUG)
Merguerian 1999	DMSA performed later than 1 month
Mersdorf 1997	Not enough data to calculate sensitivity/specificity
Mingin 2004	DMSA performed later than 1 month
Mohkam 2010	Not enough data to calculate sensitivity/specificity
Mohkam 2012	UTI definition not specified
Monakil 2013	UTI definition not specified
Montini 2008	Not enough data to calculate sensitivity/specificity
Moon 2009	Not enough data to calculate sensitivity/specificity
Muensterer 2002	Not all patients had a UTI
Muga Zuriarrain 2008	DMSA performed later than 1 month
Nafisi-Moghadam 2011	UTI definition not specified
Nammalwar 2005	UTI definition not specified
Naseri 2013	Not enough data to calculate sensitivity/specificity
Nelson 2013	UTI definition not specified
Ninos 1998	Not all patients had UTI
Orive 2010	UTI definition not specified
Otukesh 2011	Enhanced ultrasound
Otukesh 2013	Not enough data to calculate sensitivity/specificity
Paripovic 2010	Not enough data to calculate sensitivity/specificity
Pecile 1999	Gold standard was not uniformly VCUG
Pecile 2009	Gold standard was not uniformly VCUG
Pennesi 2012	VCUG only in high-risk children

Study	Reason for exclusion
Printza 2012	Gold standard was not radiographic VCUG
Puseljic 2003	UTI definition not met
Quirino 2011	UTI definition not specified
Radmayr 2001	Enhanced ultrasound
Radmayr 2002	UTI definition not specified
Risi 1990	Not enough data to calculate sensitivity/specificity
Ristola 2013	Not enough data to calculate sensitivity/specificity
Rosenberg 1990	UTI definition not specified
Rosenberg 1992	Not enough data to calculate sensitivity/specificity
Sadeghi-bojd 2013	Not enough data to calculate sensitivity/specificity
Schiavina 1988	UTI definition not specified
Schneider 1986	Not all patients had a UTI
Schneider 1997	DMSA performed later than 1 month
Sciagra 1996	DMSA timing not given
Sinha 2013	Not enough data to calculate sensitivity/specificity
Siomou 2009	Gold standard was not radiographic VCUG
Smellie 1995	UTI definition not specified
Soccorso 2010	Less than 1/5 patients had a VCUG
Sorkhi 2010	Not all patients had a UTI
Sreenarasimhaiah 1995	Not enough data to calculate sensitivity/specificity
Stokland 1996	DMSA performed later than 1 month
Strife 1989	UTI definition not specified
Subat-Dezulovic 1998	Not relevant (no data on index test or gold standard)
Sun 2013	Not enough data to calculate sensitivity/specificity
Supavekin 2013b	Not enough data to calculate sensitivity/specificity
Taheri 2013	Only ~50% of patients had a VCUG. Methods do not adequately explain why. Timing of imaging tests not specified. Numbers in tables do not match. Bladder thickness used to define an abnormal ultrasound and many children with this finding. No age range.
Tan 1988	UTI definition not met

Study	Reason for exclusion
Tappin 1989	Not enough data to calculate sensitivity/specificity
Temiz 2006	Not all patients had a UTI
Teoh 2011	DMSA timing not given
Tepmongkol 2002	Gold standard was not uniformly VCUG
Tramma 2010	UTI definition not specified
Tsai 2004	Not relevant
Tse 2009	UTI definition not specified
Valavi 2011	Not enough data to calculate sensitivity/specificity
Venhola 2010	UTI definition not specified
Verber 1988	DMSA timing not given
Wong 2010	UTI definition not specified
Wongbencharat 2013	Not enough data to calculate sensitivity/specificity
Wu 2004	Gold standard was not radiographic VCUG
Wu 2011	Gold standard was not radiographic VCUG
Zaki 2005	DMSA performed later than 1 month
Zhang 2010	UTI definition not specified
Zhang 2013	UTI definition not specified
Zhang 2014	Not all patients had a UTI
Zhao 2006	Gold standard not a radiographic VCUG (radionuclide); no UTI definition
Zocchi 1988	UTI definition not specified

DMSA - ⁹⁹Tc-dimercaptosuccinic acid; UTI - urinary tract infection; VCUG - voiding cystourethrography; VUR - vesicoureteric reflux

Characteristics of studies awaiting classification *[ordered by study ID]*

Alvarez 2007

Study characteristics
Patient sampling
Patient characteristics and setting
Index tests

Alvarez 2007 (Continued)

Target condition and reference standard(s)	
Flow and timing	
Comparative	
Notes	Cannot obtain full text of article

Maioli 1987

Study characteristics	
Patient sampling	
Patient characteristics and setting	
Index tests	
Target condition and reference standard(s)	
Flow and timing	
Comparative	
Notes	Cannot obtain full text of article

DATA

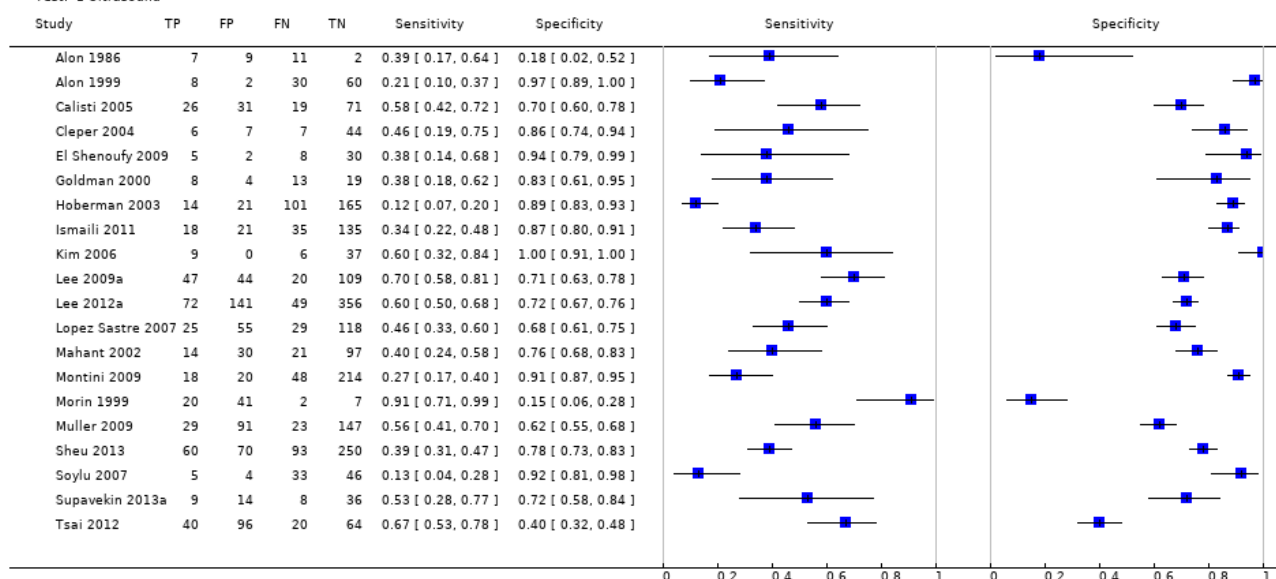
Presented below are all the data for all of the tests entered into the review.

Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 Ultrasound	20	3726
2 Ultrasound for high-grade VUR	11	2498
3 Ultrasound Renal Units	1	200
4 Ultrasound for high-grade VUR (Renal Units)	1	200
5 DMSA	19	3863
6 DMSA for high-grade VUR	10	2499
7 DMSA Renal-Units	9	1907
8 DMSA for high-grade VUR (Renal Units)	4	642

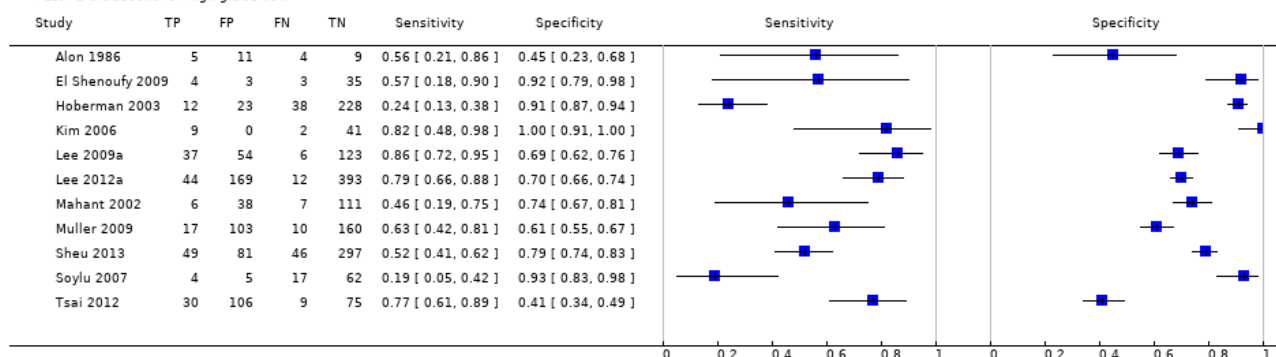
Test 1. Ultrasound.

Review: Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections
Test: 1 Ultrasound



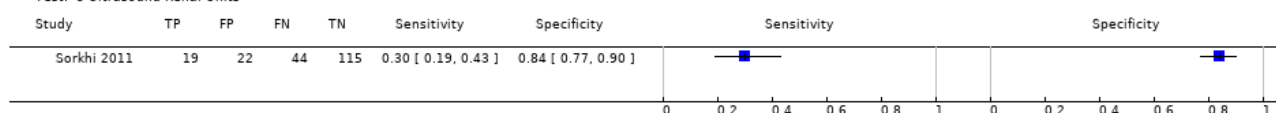
Test 2. Ultrasound for high-grade VUR.

Review: Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections
Test: 2 Ultrasound for high-grade VUR



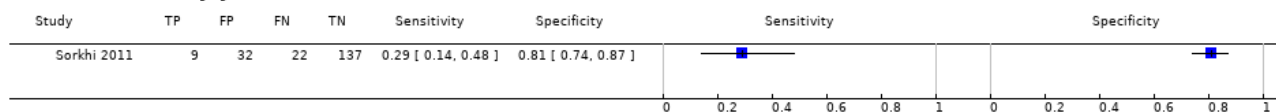
Test 3. Ultrasound Renal Units.

Review: Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections
Test: 3 Ultrasound Renal Units



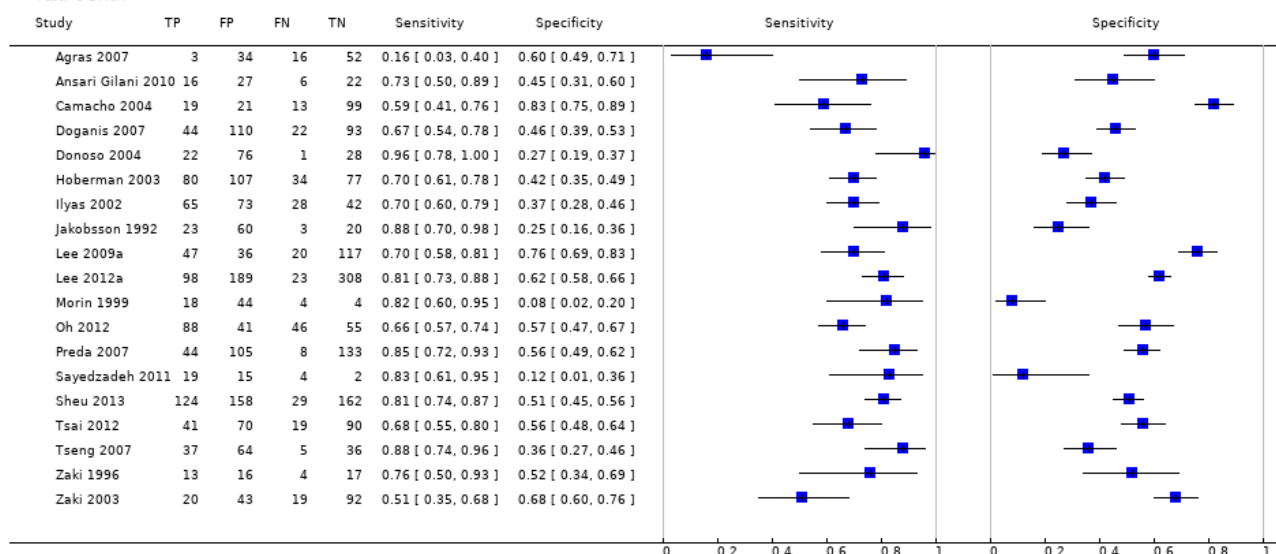
Test 4. Ultrasound for high-grade VUR (Renal Units).

Review: Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections
Test: 4 Ultrasound for high-grade VUR (Renal Units)



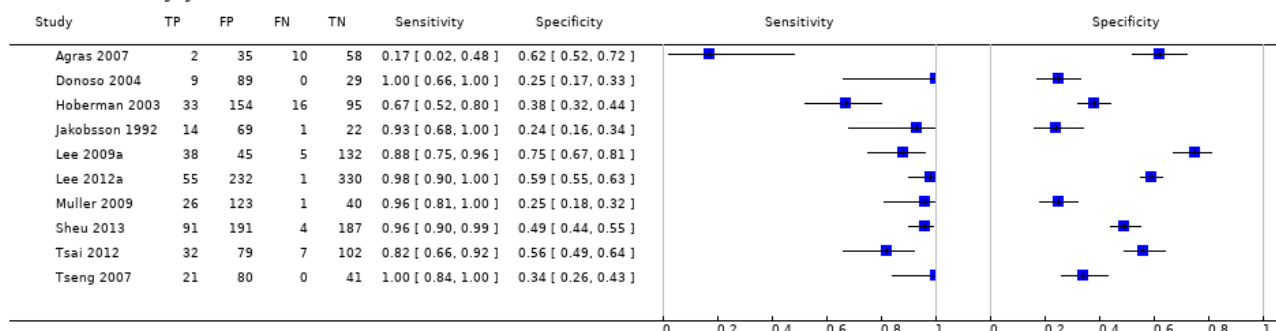
Test 5. DMSA.

Review: Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections
Test: 5 DMSA



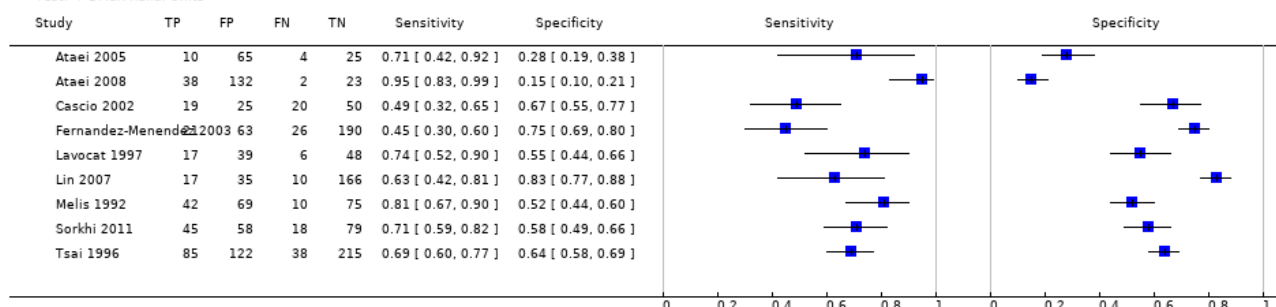
Test 6. DMSA for high-grade VUR.

Review: Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections
Test: 6 DMSA for high-grade VUR



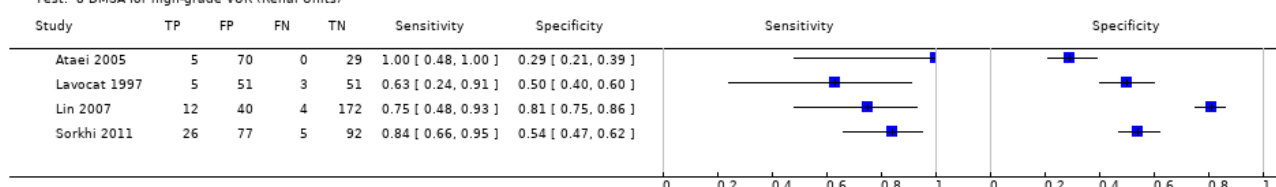
Test 7. DMSA Renal-Units.

Review: Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections
Test: 7 DMSA Renal-Units



Test 8. DMSA for high-grade VUR (Renal Units).

Review: Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections
Test: 8 DMSA for high-grade VUR (Renal Units)



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
MEDLINE	<ol style="list-style-type: none"> exp Succimer/ Organotechnetium Compounds/ Organometallic Compounds/ and Technetium/ Radionuclide Imaging/ DMSA.tw. dimercaptosuccin\$.tw. dimercapto-succin\$.tw. scintigra\$.tw. Ultrasonography/ exp Ultrasonography, Doppler/ Ultrasonography, Interventional/ (ultrasound or ultrasonogra\$ or echogr\$ or sonogr\$).tw. or/1-12 Vesico-Ureteral Reflux/ vesicoureteral reflux.tw. vesico-ureteral reflux.tw. VUR.tw. or/14-17 and/13,18

(Continued)

- 20.Vesico-Ureteral Reflux/ri
- 21.Vesico-Ureteral Reflux/us
- 22.Vesico-Ureteral Reflux/ and "Sensitivity and Specificity"/
- 23.or/20-22
- 24.or/19,23
- 25.exp Infant/ or exp Child/ or Adolescent/ or exp Puberty/ or Pediatrics/ or exp Schools/
- 26.(infant* or infancy or newborn* or baby or babies or neonat* or preterm or prematur* or post-matur* or child* or schoolchild* or school age* or preschool* or kid or kids or toddler* or adolesc* or teen* or boy* or girl* or minor or minors or pubert* or pubescen* or prepubescen* or paediatric* or pediatric* or nursery school* or kindergar* or primary school* or secondary school* or elementary school* or high school* or highschool*).tw.
- 27.or/25-26
- 28.and/24,27

EMBASE

1. succimer tc 99m/
2. succimer/
3. (dimercaptosuccin\$ or dimercapto-succin\$).tw.
4. DMSA.tw.
5. Scintigraphy/
6. scintigra\$.tw.
7. Scintiscanning/
8. Radioisotope Diagnosis/
9. Echography/
- 10.Doppler Echography/
- 11.Echotomography/
- 12.(ultrasound or ultrasonogr\$ or echogr\$ or sonogr\$).tw.
- 13.or/1-12
- 14.vesicoureteral reflux/
- 15.vesicoureteral reflux.tw.
- 16.vesico-ureteral reflux.tw.
- 17.VUR.tw.
- 18.or/14-17
- 19.and/13,18
- 20.vesicoureteral reflux/ and (diagnostic test accuracy/ or "sensitivity and specificity"/)
- 21.or/19-20
- 22.exp Child/
- 23.exp Infant/
- 24.Adolescent/
- 25.exp Adolescence/
- 26.school/
- 27.pediatrics/
- 28.child urology/
- 29.(infant* or infancy or newborn* or baby or babies or neonat* or preterm or prematur* or post-matur* or child* or schoolchild* or school age* or preschool* or kid or kids or toddler* or adolesc* or teen* or boy* or girl* or minor or minors or pubert* or pubescen* or prepubescen* or paediatric* or pediatric* or nursery school* or kindergar* or primary school* or secondary school* or elementary school* or high school* or highschool*).tw.
- 30.or/22-29
- 31.and/21,30

BIOSIS

1. TS=dimercaptosuccin*
2. TS=dimercapto-succin*
3. TS=scintigra*

(Continued)

4. TS=(ultrasound OR ultrasonogra* OR echogra* OR sonogra*)
5. TS=DMSA
6. #1 OR #2 OR #3 OR #4 OR #5
7. TS=vesico-ureteral reflux
8. TS=vesicoureteral reflux
9. TS=vesico-ureteric reflux
10. TS=vesicoureteric reflux
11. #10 OR #9 OR #8 OR #7
12. TS=(child* OR infant* OR boy* OR girl* OR school* OR adolescen* OR pediatric OR paediatric*)
13. #6 AND #11 AND #12

Cochrane Register of Diagnos-
tic Test Accuracy Studies

1. Urinary tract infection
2. VUR
3. Vesicoureteral reflux
4. #1 or #2 or #3

Appendix 2. QUADAS-2

Domain 1: Patient selection

A study was deemed as having a "high risk of bias" for this domain if:

1. The study was retrospective and included a convenience sample of patients who happened to have the index test of interest and the reference standard (i.e. the primary inclusion criteria was having had all relevant imaging tests, not having had a UTI). Because these studies were retrospective, bias cannot be ruled out. For example, performance of the reference standard may have been influenced by the results of the index test.
2. Excluded subgroups of children based on events occurring long after the diagnosis of UTI (e.g. recurrence of UTI)

A study was deemed as having a "high risk" for applicability if it Included only a subgroup of children with UTI.

1. Only patients in a restricted age range (e.g. neonates, one gender),
2. Only patients with elevated inflammatory markers (e.g. C-reactive protein, erythrocyte sedimentation rate),
3. Patients were markedly different from that of a cohort of children with UTI
4. Only high-risk patients referred for imaging

Domain 2: Index test

A study was deemed as having a "high risk of bias" for this domain if the test procedure was markedly different from usual practice or if a markedly unusual threshold was used. If the index test occurred before the reference standard, it was assumed to have been interpreted blindly. Because all studies except those which used a regular renal ultrasound and a DMSA scan as the reference standard were excluded, no studies were "high risk" for applicability.

Domain 3: Reference standard

A study was deemed as having a "high risk of bias" for this domain if the VCUG was not interpreted as per the International Reflux study criteria. Because the interpretation of the VCUG test is quite standardized, it is less prone to bias due to the lack of blinding. Accordingly, lack of blinding alone did not result in a "high risk of bias".

Because all studies included used the radiographic VCUG as the reference standard were excluded, no studies were "high risk" for applicability.

Domain 4: Flow and timing

A study was deemed as having a "high risk of bias" for this domain if

1. Not all patients received same reference standard OR
2. Excluded patients appear to have been excluded for reasons related to index test results (i.e. missing data not at random) OR
3. More than 20% of patients had missing data

Because VUR is very slow to resolve (years) and because GU anomalies uncovered by ultrasound are similarly slow to resolve or are permanent, the timing of the VCUG and RBUS are not critical. All studies in which the DMSA was conducted > 30 days were excluded. Thus, the timing of the tests in this review was of secondary importance.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: NS, RS
2. Study selection: NS, RS, SH
3. Extract data from studies: NS, RS, SH
4. Enter data into RevMan: NS, RS, SH
5. Carry out the analysis: NS, RS
6. Interpret the analysis: NS, RS, SH
7. Draft the final review: NS, RS, SH
8. Disagreement resolution: NS, RS, SH

DECLARATIONS OF INTEREST

- Nader Shaikh: none known
- Russell B Spingarn: none known
- Stephanie W Hum: none known

SOURCES OF SUPPORT

Internal sources

- None, Namibia.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title of the review from "DMSA versus Ultrasound in screening for VUR among children with a UTI" to "DMSA or ultrasound in screening for VUR among children with UTIs". We also decided to include studies in which the timing of the VCUG or RBUS was unspecified. Almost all centres we are aware of conduct these tests within the first two months after the diagnosis of a UTI. Because the results of these tests are unlikely to change within this time period, the exact timing of these tests is of secondary interest only. We had stated that we would include only children < 18 years of age. However, we later decided to include one study that included children up to 19 years of age. We did not search for ongoing studies. Because of the relatively small number of studies, meta-influence analysis was not performed. Although not specified in the protocol, we decided to include studies that reported data in terms of renal units.

INDEX TERMS

Medical Subject Headings (MeSH)

*Radiopharmaceuticals; *Technetium Tc 99m Dimercaptosuccinic Acid; Cohort Studies; Cross-Sectional Studies; ROC Curve; Radionuclide Imaging; Sensitivity and Specificity; Severity of Illness Index; Ultrasonography; Urinary Tract Infections [*complications]; Vesico-Ureteral Reflux [complications] [*diagnostic imaging]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant; Infant, Newborn; Young Adult